Epidemiological studies demonstrate that poor glycaemic control is an independent risk factor for CVD. Postprandial glycaemia has been demonstrated as a better predictor of glycated Hb, the gold standard of glycaemic control, when compared with fasting blood glucose. There is a need for more refined strategies to tightly control postprandial glycaemia, particularly in those with type 2 diabetes, and nutritional strategies around meal consumption may be effective in enhancing subsequent glycaemic control. Whey protein administration around meal times has been demonstrated to reduce postprandial glycaemia, mediated through various mechanisms including an enhancement of insulin secretion. Whey protein ingestion has also been shown to elicit an incretin effect, enhancing the secretion of glucose-dependent insulinotropic peptide and glucagon-like peptide-1, which may also influence appetite regulation. Acute intervention studies have shown some promising results however many have used large dosages (50–55 g) of whey protein alongside high-glycaemic index test meals, such as instant powdered potato mixed with glucose, which does not reflect realistic dietary strategies. Long-term intervention studies using realistic strategies around timing, format and amount of whey protein in relevant population groups are required.

Whey protein: Postprandial metabolism: Hyperglycaemia

Chronic metabolic conditions such as type 2 diabetes (T2D) currently place an unprecedented burden upon global health care systems, and vast swathes of scientific literature are devoted to understanding their aetiology and the development of strategies for prevention and treatment. In this context, the postprandial period is of significant interest to researchers due to its acute effects on the metabolic and hormonal milieu, and the adverse health effects associated with chronic exposure to an impaired meal response. Given that western populations effectively spend most of the day in the postprandial state, interventions aiming to adjust the acute meal response are pertinent to preventing the deterioration in metabolic health that may precede the onset of overt symptoms.

In the years that precede the development of T2D, a progressive transition from normal glucose tolerance to impaired glucose tolerance occurs, characterised by a decline in both insulin action and early phase insulin secretion. Hyperglycaemia ensues, with postprandial glycaemic control rather than fasting glucose appearing to deteriorate first. Evidence suggests a considerable number of individuals with normal fasting glucose have an abnormal postprandial glucose level and postprandial hyperglycaemia has been identified as an independent and continuous risk factor for CVD in diabetic and non-diabetic populations. This remains the case when fasting glucose is in the normal range.

Pharmacological agents such as metformin and thiazolidinediones are known to be effective in reducing blood glucose concentrations, with possible favourable cardiovascular effects. Their effectiveness in maintaining normoglycaemia over the long term is uncertain however,

Abbreviations: AUC, area under curve; BCAA, branched-chain amino acids; DPP-IV, dipeptidyl peptidase-IV; GI, glycaemic index; T2D, type 2 diabetes.

*Corresponding author: E. Stevenson, email emma.stevenson@newcastle.ac.uk
while significant side effects may limit use\textsuperscript{(11,12)}. The role of lifestyle in the prevention of onset and deterioration in metabolic health is therefore paramount, and evidence demonstrating that many chronic diseases are preventable through lifestyle is compelling\textsuperscript{(13–15)}. A key component of this is identifying dietary practices and food components, which reduce the risk of deterioration in metabolic health outcomes.

Dietary strategies including modification of complex carbohydrate intake or consumption of low glycaemic index (GI) diets may be beneficial in improving metabolic health outcomes\textsuperscript{(16)}, however compliance may be difficult to maintain in the long term\textsuperscript{(17)}. A wealth of epidemiological evidence associates increased daily consumption with reduced risk of metabolic disease and an inverse relationship has been demonstrated between dairy consumption and glycaemia\textsuperscript{(18,19)} as well as incidence of T2D\textsuperscript{(20,21)}. Milk and other dairy products are complex and diverse foods containing a number of key nutrients and bioactive components may synergistically contribute to reduction of disease risk\textsuperscript{(22)}. It is therefore prudent to consider the effect of isolated components in randomised controlled trials. Dairy proteins appear to play a key role in the influence of dairy consumption on metabolic outcomes, with an accumulating body of evidence supporting the beneficial effects of whey protein consumption in particular\textsuperscript{(23–25)}.

Bovine milk protein comprises of two distinct types of proteins, namely whey (approximately 20%) and casein (approximately 80%). Both whey and casein are complete proteins, however whey is a considerably richer source of the branched-chain amino acids (BCAA) leucine, isoleucine and valine\textsuperscript{(26)}, which may have important metabolic consequences. Casein is precipitated in the stomach by gastric acid resulting in coagulation and slowing of gastric emptying, whereas whey proteins are acid-soluble and rapidly emptied from the stomach and delivered to the small intestine intact\textsuperscript{(24)}. This results in a greater increase in plasma amino acids, which may be important for augmenting the postprandial response. Studies in a variety of populations have identified the capacity of whey protein to augment the postprandial insulinaemic response, with potential concomitant effects on glycaemia. The present paper will review the current evidence and provide an overview of the potential mechanisms by which whey protein consumption may influence postprandial glycaemia.

### Whey protein and postprandial glycaemia

It is likely that several mechanisms interact to affect postprandial glycaemia, with evidence suggesting that whey lowers glucose via insulin-dependent and insulin-independent mechanisms\textsuperscript{(27)}. Although not fully understood, it appears that whey protein enhances postprandial insulinemia via direct and indirect pathways. It is well established that protein, or more specifically amino acids, stimulate insulin secretion\textsuperscript{(28)}. This effect is present in healthy individuals\textsuperscript{(29)} and in those with T2D (who have a blunted insulin response to increases in plasma glucose concentration), where coingestion of protein with carbohydrate amplifies the insulin response\textsuperscript{(30,31)}. Whey protein is a rich source of essential amino acids, known to be potent insulin secretagogues\textsuperscript{(32)}. Leucine is of particular interest in this regard, exerting acute and chronic effects at multiple regulatory sites including pancreatic β-cells, liver, muscle and adipose tissue to influence glucose homeostasis\textsuperscript{(33)}.

Previous studies using β-cell lines or incubated primary islet cells have described two separate pathways where leucine directly stimulates insulin secretion via increases in the intracellular ATP:ADP ratio within β-cells. Firstly, intracellular catabolism of leucine acts to increase energy status via its deaminated metabolite α-ketoisocaproic acid, which is converted to acetyl-CoA before entering the tricarboxylic acid cycle\textsuperscript{(33–35)}. Secondly, leucine can allosterically activate glutamate dehydrogenase, which converts glutamate to α-ketoglutarate, an intermediate in the tricarboxylic acid cycle\textsuperscript{(33,36,37)}. The subsequent increase in ATP results in closure of ATP-sensitive potassium channels, which has the effect of depolarising the cell membrane, generating an influx of calcium ions. Oscillations in membrane potential are accompanied by oscillations in cytosolic calcium concentration and subsequent exocytosis of secretory granules, which discharge their contents (insulin, C-peptide and some proinsulin) into the extracellular space\textsuperscript{(38)}. It has also been proposed that some amino acids can directly depolarise the cell membrane through co-transport with Na\textsuperscript{+}\textsuperscript{(34,39)}, thus activating voltage-dependent calcium channels resulting in subsequent insulin secretion as described earlier. Additionally, BCAA can activate the mechanistic target of rapamycin pathway via stimulation of P70 S6 kinase\textsuperscript{(33,40), with leucine described as the most effective in this regard\textsuperscript{(34)}}. This activation of the mechanistic target of rapamycin mitogenic signalling pathway is associated with mitochondrial signals generated by leucine metabolism, leading to stimulation of protein synthesis and enhanced β-cell function\textsuperscript{(41)}.

When intact whey protein or a mixture of amino acids including BCAA were administered to healthy individuals (combined with 25 g glucose), both drinks raised insulin concentrations similarly, suggesting that the action of whey on postprandial glycaemia is largely associated with its BCAA content\textsuperscript{(42)}. However, the glucose-dependent insulino tropic peptide response was 80% greater following intact whey compared with glucose control, whereas it was not different for the amino acid mixtures. This is indicative of bioactive peptides present in intact whey, or formed during digestion, influencing the incretin response. Indeed, whey also stimulates glucagon-like peptide-1 release in healthy males\textsuperscript{(43)}. Both hormones have strong insulino tropic effects\textsuperscript{(43)}, therefore whey stimulated incretin release may be responsible for an indirect influence on the insulin response, an effect observed \textit{in vitro}\textsuperscript{(44)}.

The efficacy of the incretin hormone response is diminished by rapid degradation to inactive forms by the dipeptidyl peptidase-IV (DPP-IV) enzyme\textsuperscript{(45)}. Dairy proteins, including whey, have emerged as potential endogenous inhibitors of DPP-IV; however, evidence in
human subjects is limited. Administration of whey has been associated with a significant reduction in DPP-IV activity in mice (46), while a peptide identified from whey β-lactoglobulin hydrolysate is associated with moderate DPP-IV inhibition in vitro (47). In human subjects with T2D, consuming 50 g whey protein compared with water prior to a high GI breakfast reduced postprandial glycaemia while stimulating insulin and glucagon-like peptide-1 responses; however no differences in DPP-IV activity were detected (48). One explanation may be that DPP-IV inhibition in the small intestine may not have been detectable in the plasma, with the possibility that this is another indirect mechanism where whey exerts an effect on insulin secretion.

The most likely mediator of insulin-independent actions of whey on glycaemia is a result of modulation of gastric emptying, since slowing of gastric emptying can diminish postprandial glucose excursions (49,50). The addition of whey protein to a carbohydrate load reduces postprandial glucose while displaying delayed gastric emptying (51), and addition of whey to a preload has been reported to slow gastric emptying of a subsequent meal in healthy (52) and diabetic (53) populations. The gastric emptying and incretin related properties of whey consumption in the context of attenuating postprandial glucose excursions appear to be interdependent, as glucagon-like peptide-1 also slows gastric emptying and suppresses glucagon secretion (25).

**Acute intervention studies**

The number of published acute studies investigating the effects of whey protein consumption on postprandial responses has increased considerably in recent years. A summary of these studies in normal-weight, overweight/obese and T2D populations is provided in Table 1. Studies in a variety of populations have identified the capacity of whey protein to augment the postprandial insulinaemic response, with potential concomitant effects on glycaemia. Studies with overweight or T2D populations are fewer in number than those with healthy sample groups, and it remains unclear whether the magnitude of the insulinitropic effect following whey supplementation is sufficient to consistently reduce postprandial glycaemia in insulin resistant individuals, where hyperinsulinaemia may be commonplace.

Zafar et al. (54) investigated the effects of 25 g whey protein or glucose, or a combination of both (50 g), on postprandial glycaemia for 120 min in fifteen normal-weight and fifteen overweight young females. Whey protein was effective in reducing postprandial glycaemia compared with glucose and glucose with whey, while the latter condition suppressed blood glucose compared with control. Glucose area under curve (AUC) was 16% higher following the pure glucose drink in overweight compared with normal-weight participants, however this disparity in glucose tolerance between groups was corrected when whey protein was administered, with glucose attenuated to similar levels in both groups following whey protein beverages. The authors hypothesise that such an effect may be due to an enhancement of insulin sensitivity by whey protein in overweight participants; however insulin concentrations were not assessed in this study, making this a speculative assumption. Such an effect has, however, been observed following chronic whey protein consumption in both rats (55) and human subjects (56).

A dose–response relationship between whey protein load and post-meal glucose reduction has been observed in several studies in normal weight (52,57) and obese populations (58). Both studies in lean healthy individuals observed a linear effect of glucose reduction with whey protein loads ranging 5–40 g (59) and 4.5–18.0 g (60), however, differential patterns in insulin response were reported between studies, which may be the result of a number of fundamental differences in study design. Akhavan et al. (59) administered whey as a preload 30 min before consumption of a mixed-macronutrient meal, whereas Gunnerud et al. (57) did not use a preload design. The addition of 18 g whey to 25 g glucose has previously been found to significantly reduce glycaemia with a concomitant increase in insulin AUC (61), and it has been proposed that amino acid availability may potentiate the increased insulin response. This is an attractive theory since plasma amino acids also increased in a dose-dependent manner in this study, while a previous investigation revealed that a combination of whey and free amino acids induced a rapid insulinoergic effect, which influenced early glycaemia (59).

A limited number of studies have assessed the glycemic response following whey supplementation in non-diabetic overweight or obese populations. A significant reduction in glucose AUC was observed over 180 min following consumption of a 55 g liquid protein preload in comparison with lactose and glucose controls in overweight or obese men (BMI ranging from 26.8 to 40.4 kg/m²), however insulin concentrations were not affected by condition (60). It is important to note that data for whey and casein protein preloads were pooled together and therefore the differential effects of whey and casein supplementation on a variety of markers (56,61) cannot be distinguished. Nevertheless, the findings of Pal et al. (62) support the observations described earlier. This group reported a 16% reduction in post-meal glycaemia over 360 min in a group of overweight or obese postmenopausal females following 45 g whey protein compared with an energy-matched glucose control. This intervention did not influence post-meal insulinemia, indicating that milk-derived proteins may influence plasma glucose via insulin-independent mechanisms or via temporal changes in insulin sensitivity. Key differences exist in the design of these studies therefore this may influence any direct comparisons. Pal et al. (62) administered protein alongside a mixed macronutrient breakfast meal, simulating the effect of consuming a realistic breakfast meal (bread roll with margarine and spread) with additional protein, which may be a more ecologically valid method than the provision of a test beverage only (60).

In patients with T2D, substituting lean ham and lactose with the equivalent amount (18-2 g) of whey protein in high GI meals significantly increased the insulin response following both breakfast (18%) and lunch.
Table 1. Summary of acute randomised trials investigating the effect of whey protein consumption on postprandial glycaemia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Design</th>
<th>Supplementation</th>
<th>Comparator</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal-weight participants</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Akhavan et al.[52]</td>
<td>Healthy: males (n 16)</td>
<td>Randomised, crossover.</td>
<td>Experiment 1: WP</td>
<td>Experiment 1: Control (flavoured water)</td>
<td>Experiment 1: 10–40 g WP reduced post-meal blood glucose concentration and AUC.</td>
</tr>
<tr>
<td></td>
<td>Age: 22 (SE 1) years BMI: 22.6 (SE 0.4) kg/m²</td>
<td>Preloads with 300 ml water 30 min before:</td>
<td>(10, 20, 30, 40 g)</td>
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<tr>
<td></td>
<td>Healthy: nine females, twelve males (n 21)</td>
<td>Experiment 1: Ad libitum pizza meal</td>
<td></td>
<td>Experiment 2: Control (flavoured water)</td>
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</tr>
<tr>
<td></td>
<td>Age: 22 (SE 1) years BMI: 22.1 (SE 0.5) kg/m²</td>
<td>Experiment 2: Standard pizza meal</td>
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<td>Experiment 2: WPH (10 g)</td>
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<tr>
<td></td>
<td></td>
<td>WP (10, 20 g)</td>
<td></td>
<td>Glucose (10, 20 g)</td>
<td>WP slowed pre-meal gastric emptying vs control and 10 g glucose.</td>
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<td></td>
<td>Both WP and glucose (10 and 20 g) reduced post-meal glycaemia.</td>
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<td></td>
<td></td>
<td>Over 230 min WP gave lower mean plasma glucose, insulin and C-peptide, but higher GLP-1 compared with glucose preloads.</td>
</tr>
<tr>
<td>Akhavan et al.[27]</td>
<td>Healthy: males (n 10)</td>
<td>Randomised, single-blind, crossover,</td>
<td>WP (20 g)</td>
<td>Control (flavoured water)</td>
<td>Post-breakfast insulinaemia was greater when WP added to breakfast.</td>
</tr>
<tr>
<td></td>
<td>Age: 18–29 years BMI: 18.5–29.4 kg/m²</td>
<td>Preloads with 300 ml 30 min before</td>
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<td></td>
<td>No difference in post-breakfast glycaemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>standardised pizza meal.</td>
<td></td>
<td></td>
<td>No post-lunch effects of condition on glycaemia or insulinaemia.</td>
</tr>
<tr>
<td>Allerton et al.[78]</td>
<td>Healthy: males (n 10)</td>
<td>Randomised, crossover.</td>
<td>WP (16.2 g)</td>
<td>White wheat bread (control)</td>
<td>Glucose iAUC was reduced after all protein meals compared with control.</td>
</tr>
<tr>
<td></td>
<td>Age: 24 (SE 1) years BMI: 24.5 (SE 0.7) kg/m²</td>
<td>Standard breakfast (93 g CHO, 9 g protein)</td>
<td></td>
<td>Casein (16.8 g)</td>
<td>Insulin response was significantly higher after WP.</td>
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<tr>
<td></td>
<td></td>
<td>served with or without WP or breakfast omitted. Standard lunch served 180 min post.</td>
<td></td>
<td>Bovine milk</td>
<td>Early phase plasma AA were correlated to insulin and incretin secretion.</td>
</tr>
<tr>
<td>Gunnerud et al.[79]</td>
<td>Healthy: three females, six males (n 9)</td>
<td>Randomised, crossover.</td>
<td>WP (9 g)</td>
<td>Human milk (all CHO matched)</td>
<td>All protein drinks reduced the glycaemic response in the first 60 min.</td>
</tr>
<tr>
<td></td>
<td>Age: 22–30 years BMI: 25.8 (SE 3.4) kg/m²</td>
<td>Test meals served as breakfast.</td>
<td></td>
<td>WP +10 AA, WP +10 AA, SP, SP +5 AA</td>
<td>No differences for insulinaemic indices.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>SP +5 AA (all energy matched)</td>
<td>The early insulin response (0–15 min iAUC) correlated positively with plasma AA, GLP-1, GIP and glycaemic profile.</td>
</tr>
<tr>
<td>Gunnerud et al.[59]</td>
<td>Healthy: nine females, five males (n 14)</td>
<td>Randomised, single-blind, crossover.</td>
<td>WP (9 g)</td>
<td>Control (water)</td>
<td>Linear dose-response relationships found between WP dose and postprandial glycaemia, insulinaemia and AA.</td>
</tr>
<tr>
<td></td>
<td>Age: 20–28 years BMI: 21.9 (SE 0.6) kg/m²</td>
<td>Standard breakfast (50 g CHO, 13 g protein)</td>
<td></td>
<td></td>
<td>18 g and 9 g WP significantly reduced glycaemia.</td>
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<tr>
<td></td>
<td></td>
<td>with test drinks (immediately pre-meal).</td>
<td></td>
<td></td>
<td>18 g increased insulin response.</td>
</tr>
<tr>
<td>Gunnerud et al.[57]</td>
<td>Healthy: seven females, five males (n 12)</td>
<td>Randomised, single-blind, crossover.</td>
<td>WP (4.5, 9.0, 18.0 g)</td>
<td>Control (water + 25.0 g glucose)</td>
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</tr>
<tr>
<td></td>
<td>Age: 20–23 years BMI: 22.9 (SE 0.7) kg/m²</td>
<td>Test drinks (250 ml) served as breakfast.</td>
<td>(combined with 25.0 g glucose)</td>
<td></td>
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</tr>
</tbody>
</table>
Table 1. (Cont.)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Design</th>
<th>Supplementation</th>
<th>Comparator</th>
<th>Key outcomes</th>
</tr>
</thead>
</table>
| Nilsson et al. (42) | Healthy: six females, six males (n = 12)  
Age: 20–30 years  
BMI: 22.4 (± 0.6) kg/m² | Randomised, crossover.  
Test drinks (250 ml) provided as breakfast. | WP (18 g) (combined with 25 g glucose) | Lysine and threonine  
Leucine, isoleucine and valine  
Leucine, isoleucine, valine, lysine and threonine (all with 25 g glucose)  
Control (25 g glucose) | Consumption of WP resulted in 56% smaller glucose AUC and 60% larger insulin AUC than reference drink.  
WP drink gave 80% greater GIP response, whereas drinks containing free AA did not significantly affect GIP secretion. |
| Silva Ton et al. (79) | Healthy: six females, four males (n = 10)  
Age: 25 (± 1) years  
BMI: 22.0 (± 0.8) kg/m² | Randomised, crossover.  
Test preload 30 min prior to consumption of 25 g glucose. | WP (0.5 g/kg BM) | Control (flavoured water)  
SP (0.5 g/kg BM)  
Egg albumin (0.5 g/kg BM) | WP and SP reduced glucose iAUC by 56.5% and 44.4% compared with control, respectively. |
| Hoeffe et al. (51) | Healthy (15) and prediabetes (15): five females, twenty-five males (n = 30)  
Age: Healthy – 26 (± 1), prediabetes – 62 (± 2) years  
BMI: Healthy – 23.9 (± 0.5), prediabetes – 29.0 (± 1.5) kg/m² | Randomised, single-blind, crossover.  
Test drinks served and samples taken 240 min postprandially. | WP (50 g) (combined with 50 g maltodextrin) | Control (50 g maltodextrin)  
Casein (50 g with maltodextrin 50 g) | WP and casein similarly reduced postprandial glucose excursions in healthy and prediabetic participants.  
Both proteins increased plasma insulin despite simultaneous increases in glucagon concentrations. |
| Zafar et al. (54)  | Healthy: females (n = 12)  
Age: 22 (± 5) years  
BMI: 22.6 (± 2.4) kg/m²  
Healthy (15) and overweight (15): females (n = 30)  
Age: 22 (± 5) years  
BMI: Healthy – 21.5 (± 2.1), overweight – 30.7 (± 2.5) kg/m² | Randomised, crossover.  
Test beverages (300 ml) followed by ad libitum pizza meal (180 min post).  
Randomised, crossover.  
Sweetened beverages (300 ml) consumed, samples taken for 120 min. | WP (25 g) | WP (25 g) + glucose (50 g)  
Glucose (50 g)  
Glucose (75 g)  
WP (25 g) + glucose (25 g)  
Glucose (25 g) | Peak blood glucose and IAUC were reduced after WP and WP supplemented glucose in both normal weight and overweight participants. |
| Overweight: males (n = 19)  
Age: 53 (± 6) years  
BMI: 32.1 (± 3.7) kg/m² | Randomised, single-blind, crossover.  
Liquid preloads consumed followed after 180 min by ad libitum buffet meal. | WP (55 g) | Casein (55 g)  
Lactose (56 g)  
Glucose (56 g) control | Significant reduction in glucose AUC observed following consumption of protein preload in comparison with lactose and glucose.  
Small increase in BCAA after WP compared with casein.  
Glucose was reduced after WP and casein compared with control.  
Appearance of TAG in the blood decreased after the WP meal compared with control and casein by 21% and 27%, respectively. |
| Pal et al. (60)  | Overweight and obese: females (n = 20)  
Age: <66 years  
BMI: 25–40 kg/m² | Randomised, single-blind, crossover.  
Test drinks (about 400 ml) consumed with mixed-macronutrient breakfast. | WP (45 g) | Sodium caseinate (45 g)  
Control (glucose 45 g) (matched for energy) | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participant Details</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen et al. (58)</td>
<td>Obese: three females, seven males (n 10) Age: 44 (±9) years BMI: 33.6 (±4.8) kg/m²</td>
<td>Randomised, crossover. Drinks (250 ml) provided as breakfast.</td>
<td>5, 10, 20 g intact WP + peptides (with 50 g glucose)</td>
<td>Control (50 g glucose)</td>
</tr>
<tr>
<td>T2D participants Clifton et al. (80)</td>
<td>Prediabetes (11) and T2D (13): 11 females, 13 males (n 24) Mean age: 60 years Mean BMI: 32 kg/m²</td>
<td>Randomised, crossover. Liquid preloads (150 ml) followed after 15 min by standardised CHO-based breakfast.</td>
<td>WP (17 g) with 5 g added fibre (guar)</td>
<td>Control (water)</td>
</tr>
<tr>
<td>Frid et al. (63)</td>
<td>T2D: six females, eight males (n 14) Age: 27–69 years BMI: 26.2 (±3.1) kg/m²</td>
<td>Randomised, crossover. High GI breakfast and lunch 4 h post breakfast, with trial-dependent addition of WP or ham and lactose.</td>
<td>WP (18.2 g) with both meals = 36.4 g in total</td>
<td>Ham and lactose (matched for protein and CHO content)</td>
</tr>
<tr>
<td>Jakubowicz et al. (48)</td>
<td>T2D: six females, nine males (n 15) Age: 64 (±1) years BMI: 29.7 (±1.2) kg/m²</td>
<td>Randomised, crossover. Test drinks (250 ml) consumed as a preload 30 min prior to a high GI breakfast.</td>
<td>WP (50 g)</td>
<td>Control (water)</td>
</tr>
<tr>
<td>Ma et al. (53)</td>
<td>T2D: seven females, one male (n 8) Age: 58 (±3) years BMI: 28.6 (±1.3) kg/m²</td>
<td>Randomised, crossover. Preload administered 30 min before high GI meal (59.1 g CHO). WP added to preload, meal or not added.</td>
<td>WP in preload (55 g) WP in meal (55 g)</td>
<td>Control</td>
</tr>
</tbody>
</table>

Increasing doses of intact WP and peptides decreased blood glucose iAUC in a dose-dependent manner.

Peak glucose was reduced by 2.1 mmol/l at 45 min. Mean glucose over 3 h was reduced by 0.8 mmol/l. No difference between those with diabetes or prediabetes. Insulin AUC 31% higher after breakfast and 57% higher after lunch with WP. Glucose AUC similar after breakfast but reduced by 21% after lunch with WP. GIP response higher after WP ingestion. Blood glucose levels reduced by 28% after WP preload. Insulin and GLP-1 responses significantly higher following WP. DPP-IV activity not different between trials. Gastric emptying was slowest after the WP preload, and slower after WP meal than control. Glucose iAUC reduced for WP preload and WP meal compared to control. GIP and insulin were higher during both WP trials than control, GLP-1 was only higher after the WP preload.

AA, amino acids; AUC, area under curve; BCAA, branched-chain amino acids; BM, body mass; CHO, carbohydrate; DPP-IV, dipeptidyl peptidase IV; GI, glycaemic index; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; SP, soy protein; T2D, type 2 diabetes; WP, whey protein; WPH, whey protein hydrolysate.
(49%), however glycaemia was similar following the breakfast meal, and only reduced after lunch (21%)\(^{(63)}\). It is possible that the post-breakfast increase in circulating insulin was not sufficient to overcome the greater insulin resistance observed in the post-absorptive state\(^{(64)}\). The post-lunch reduction in glycaemia is comparable with the 28% reduction in glucose AUC observed alongside a simultaneous 105% increase in insulin AUC by Jakubowicz et al\(^{(48)}\). This study compared 50 g whey protein consumption with a control (water) drink before a high GI breakfast in participants with T2D. The higher dose of protein and the fact that it was administered as a preload 30 min prior to the breakfast meal in the latter study, in addition to the fact that it was a single meal test, means that these findings are not directly comparable. Despite this, the effect observed on postprandial glycaemia in both studies was greater than that detected over the same time period (180 min) following administration of nateglinide, a pharmacologic rapid-acting insulin secretagogue\(^{(65)}\), emphasising the potential of dietary strategies for glycaemic management in individuals with impaired glucose metabolism. In a further study in participants with T2D, similar reductions in post-meal glycaemia were observed whether 55 g whey was given before (30 min) or alongside a high GI meal compared with no supplementation\(^{(53)}\). Rate of gastric emptying was also measured as part of this protocol and was inhibited by the presence of whey; however there was no evidence that the difference in emptying rates between the whey preload and whey in meal trials was reflected in postprandial glycaemia.

**Longer-term intervention studies**

Although many of the mechanistic pathways are yet to be fully elucidated, the potential benefits of whey ingestion have been described earlier, which encourages the possibility that metabolic health status may be improved if it is consumed chronically. Studies assessing the longer-term effects of whey supplementation are relatively few in number, with only one study having been carried out in normal-weight participants\(^{(66)}\) and a small number in overweight/obese\(^{(56,67-69)}\) or diabetic\(^{(70)}\) individuals.

The majority longer-term studies have been designed to address the impact of whey protein supplementation on appetite regulation and body weight management with limited data published on glycaemic control. It is important to consider however that reductions in body weight will positively impact insulin sensitivity and therefore have a direct effect on postprandial glycaemic control. To date, no longer-term whey protein intervention studies have measured postprandial glycaemic control but have included fasting glucose and insulin measurements. Two studies that involved supplementation of about 55 g/d whey protein for 12 and 23 weeks reported reductions in fasting insulin concentrations compared with carbohydrate supplemented groups, without reduction in fasting glucose, indicating an improvement in insulin sensitivity\(^{(56,68)}\). The mechanisms explaining this improvement are unclear as this effect was independent of any change in body or fat mass in the latter study; however this effect of chronic whey supplementation on insulin sensitivity is supported by evidence from rat studies\(^{(55,71)}\).

The limited evidence to date appears to show that chronic supplementation of the diet with whey protein is associated with possible metabolic health benefits including improved fasting lipid profile and insulin sensitivity, with possible effects on food intake and body mass. Caution must be taken when interpreting these findings however, as longer-term trials lack the control over extraneous variables, which exist in the laboratory environment. Variations in free-living physical activity or energy intake must also be considered in longer-term trials.

**Implications for future research**

Presently, many studies involving whey protein consumption have utilised high GI, carbohydrate-rich test meals such as powdered potato with\(^{(53)}\) or without\(^{(63)}\) additional glucose, or have mixed glucose into a whey protein beverage\(^{(42,57,58)}\) served as a test breakfast. This enables assessment of the efficacy of whey to attenuate greatly elevated postprandial glycaemia; however it may be valuable to investigate the response following consumption of whey with realistic breakfast-type foods. The consumption of test beverages in place of solid foods may also have implications when assessing appetite, since satiation is initially affected by sensory features\(^{(72)}\).

There is a dearth of studies investigating the addition of whey to a meal as a supplemental strategy. A number of well controlled studies have matched comparison treatments for energy\(^{(73,74)}\) or macronutrient content\(^{(75,76)}\); however adherence in a naturalistic setting may be easier when adding protein before or alongside a meal, rather than substituting it for other nutrients in that meal. Similar designs have supplemented whey by adding it to glucose\(^{(54,58)}\) or maltodextrin\(^{(51)}\), but examples of addition to mixed-macronutrient meals are lacking.

The balance between providing an efficacious dose to reduce postprandial hyperglycaemia, ensuring palatability, and avoiding overconsumption of excess energy, should be carefully considered when designing studies. Studies in overweight/obese non-diabetic populations have all supplemented 45–55 g protein. A 45 g whey protein preload, as administered by Pal et al.\(^{(62)}\), contains about 750 kJ (about 180 kcal) which, if consumed regularly, may have a detrimental impact on energy balance.

To the author’s knowledge, only one study\(^{(53)}\) has investigated the effect of timing of whey protein before or alongside a meal on subsequent metabolic responses. Several studies have administered whey at a set time before a standardised or \textit{ad libitum} meal under all conditions, while fewer studies have administered whey protein alongside or immediately prior to a test meal. The large variation in preload timings (15–180 min) makes direct comparison of the most efficacious supplementation strategy problematic.

Further research is needed to develop optimal chronic supplementation strategies that can be incorporated into
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the diet in a free-living setting. Additionally, the implementation of longer-term supplementation protocols would allow assessment of potential negative consequences of whey protein supplementation on metabolic health. Increased postprandial insulinemia in the absence of a reduction in glycaemia is suggestive of compromised insulin sensitivity, an effect that has previously been observed following acute whey protein ingestion. Thus there is potential for the chronic exposure to the insulinotropic effects of whey protein to have a desensitising effect on sites of insulin action, which would have a detrimental effect on the prevention of metabolic disease.

Conclusions

Acute whey protein supplementation around meal times appears to improve postprandial glycaemia in normal weight, overweight and obese and T2D patients. In order for this to become a therapeutic strategy, further long-term intervention studies using realistic doses of whey protein provided in a format that can be incorporated easily into normal dietary practices are required.

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Authorship

E. J. S. and D. M. A. are solely responsible for the preparation of this manuscript.

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