INTRODUCTION

Globally, continuous glucose monitoring is changing the landscape of type 1 diabetes clinical management. The increasing, widespread use of this technology has been accompanied by an unprecedented level of interest in the dynamics of the postprandial glycaemic profile and in turn, a demand for clinical explanations for aberrant postprandial glycaemic patterns.1

To manage postprandial glycaemia in practice, insulin is administered prior to meal consumption at a dose that is adjusted to the carbohydrate content of the meal.2 Often, despite accurate carbohydrate counting and insulin dose calculation, there is dysglycaemia.3 Research has identified a significant contribution of other dietary factors, including fat and protein to this postprandial glycaemic variability.4,5 It has been demonstrated that fat and/or protein when consumed in
combination with carbohydrate increase postprandial glycaemia and delay gastric emptying leading to a lag in glucose absorption.\textsuperscript{6,7} In the absence of appropriate insulin adjustment/s, this manifests clinically, as late, sustained postprandial hyperglycaemia.\textsuperscript{4,8}

International clinical guidelines now advise that in addition to carbohydrate, children and adults with type 1 diabetes receive education on the glycaemic impact of fat and protein and tailor their insulin dose and delivery according to the total meal macronutrient composition.\textsuperscript{2,9} The provision of care, consistent with these guidelines, has the potential to improve postprandial glycaemic control; however, these guidelines lack comprehensive dosing recommendations.

Therefore, the objective of the present systematic review was to identify and report the efficacy of insulin dosing strategies currently used for fat and fat and protein meals in type 1 diabetes.

2 | METHODS

This review was conducted following a protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO, ID:CRD42019145654) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.\textsuperscript{10}

2.1 | Data sources and search strategy

A systematic literature search of four relevant biomedical databases was undertaken. The search was developed in Medline and adapted as required to EMBASE, CINAHL Complete and the Cochrane Central Register of Controlled Trials. The search strategy was designed to address the following research question: What insulin dosing strategies are used for dietary fat and a combination of dietary fat and protein in type 1 diabetes?

Terms were divided into three broad categories: (1) type 1 diabet* or diabetes type 1 or diabetes mellitus, type 1 or insulin depend* or p?ediatric diabet* or Type 1 Diabetes or iddm AND (2) dietary fat* or fat* or pizza AND (3) insulin dos* or bolu* or dual wave. The search was limited to human studies, published in the English language between March 1995 and February 2021. The start date of March 1995 was purposely selected because this was the date that the first rapid-acting insulin, Lispro was introduced to the market (USA). There was no restriction placed on the study population (race, age, sex or presence of co-morbidities). Citations and abstracts of all publications retrieved from these searches were exported into EndNote reference management software (EndNote X9.2, Clarivate Analytics, Pennsylvania, United States).

2.2 | Study selection

Following an initial review of publication title to exclude duplicate records, two review authors (T.S. and A.M.) independently completed a two-stage review process using Covidence systematic review management software (Veritas Health Innovation, Melbourne, Australia). In stage 1, titles and abstracts of all retrieved records were screened for obvious exclusions. In stage 2, the reviewers assessed full-text versions of the remaining papers against pre-specified inclusion criteria. At each review stage, disagreements regarding the inclusion of a paper/s were resolved independently by a third review author (C.S.). Studies included in the review had to be randomised controlled trials. The studies had to quantitatively measure the effects of an insulin dosing intervention for fat and protein or fat meals on postprandial glycaemia and report on at least one of the following outcomes: mean glucose, area or incremental area under the glucose curve (AUC or iAUC), time spent in the postprandial glucose target range or hypoglycaemic events. Studies that were available only in abstract form, studies that measured the effects of an insulin dosing intervention for protein meals where fat was not considered (evaluated previously by our group),\textsuperscript{11} studies that included mixed participant populations where the outcomes for the type 1
diabetes population could not be delineated or studies that were limited to, or included pregnant women with type 1 diabetes were excluded.

2.3 Data extraction and quality assessment

Data extraction was carried out by review author T.S. using a custom form. Data extraction variables included publication title, year of publication, journal, study location and setting, study design, sample size and duration, population description (mean age, age range, sex, mean diabetes duration, mean HbA1c, insulin therapy, insulin type, obese/non-obese) intervention, insulin protocol (method of dose calculation, method and duration of postprandial glucose monitoring), test meal (type and composition) main glycaemic outcomes reported, definition of main outcomes, key finding/s and funding source. For each included study, the evidence presented was assessed for selection, performance, detection, attrition and reporting biases as well as any other biases following the criteria outlined in the Cochrane Risk of Bias Assessment Tool for Randomized Controlled Trials.12

3 RESULTS

3.1 Database search

The search identified 472 potentially relevant studies. After the exclusion of 172 duplicate records, 300 records were screened by title and abstract. A further 269 records were excluded leaving a remaining 31 studies to be assessed for eligibility. A total of 18 published studies were included in this review (see Figure 1). The primary reasons for exclusion were incorrect study design (n = 4) or the paper was available only in abstract form (n = 9).

3.2 Study characteristics

The included studies represented 16 full-text articles and two short reports. All characteristics of the included studies are presented in Table S1. Studies were published from 2002 to 2021 and represented 381 participants with samples ranging in size from 7 to 42. The majority of studies were conducted in the clinic (n = 12).5,13–23 Seven of the included studies were carried out in adults (>18 years),13–15,17,18,21 one...
in adolescents (12–18 years), three in children and adolescents (4–17 years), three in adolescents and adults (13–28 years) and four in children, adolescents and adults (6–21 years).

### 3.2.1 | Insulin therapy

The majority of studies (15 out of 18) included participants only using insulin pump therapy (IPT). Of these, two studies specified the use of sensor-augmented IPT. The remaining three studies included participants only using multiple daily injection (MDI) therapy. All studies used rapid-acting meal insulin. Twelve of the included studies reported optimising participants’ insulin doses prior to starting the study.

### 3.2.2 | Postprandial glucose measurement

To measure postprandial glucose levels six studies used continuous glucose monitoring, three used venous blood testing, six used capillary blood testing and a further three studies used a combination of continuous glucose monitoring and capillary blood testing. Studies measured glucose for 3, 4, 5, 6, 10 and 18 h after meal consumption.

### 3.2.3 | Fat and protein loads

Studies that added fat to control meals (n = 3) added 32–50 g of fat and studies that added fat and protein to control meals (n = 3) added 7–35 g of fat and 12–27 g of protein. The amount of fat in meals across all studies ranged from 2 to 79 g and included sources such as butter, margarine, cream, cheese, whole milk, fried foods (chicken, fish and chips), olive oil, avocado, peanuts and eggs. Eleven of the included studies evaluated fat in combination with protein.

### 3.2.4 | Blinding

Only two studies reported the use of blinding. One study described a triple-blinded design. The other study blinded participants to the insulin infusion rate and the test meal; however, the investigators acknowledged that participants could potentially deduce the test meal.

### 3.3 | Additional insulin

Of the 18 included studies, 13 studies gave additional insulin to manage postprandial glycaemia following fat and fat and protein meals. These studies used different methods to determine insulin requirements for dietary fat and protein (Table S1).

#### 3.3.1 | Proportional integral derivative control algorithms

Two studies added fat and fat and protein to control meals and used proportional integral derivative control algorithms to adjust the basal insulin infusion rate at 1–10 min intervals postprandially, based on the rate of change of sensor glucose. A mean additional insulin requirement equivalent to 42% ICR (range: −17% to +108%) for 50 g of fat, 43% ICR (16%–118%) for 32 g of fat and 39% ICR (5%–120%) for 35 g of fat and 27 g of protein was demonstrated.

#### 3.3.2 | Model predictive bolus algorithm

Using the same model, predictive bolus algorithm across two separate studies, Bell et al. found that for a high-fat, high-protein meal, a mean insulin dose increase of 65% ICR (17%–124%) was necessary to optimise postprandial glycaemia over 6 h, whereas over 5 h, high-fat meals containing 22, 42 and 62 g fat with fixed protein and carbohydrate required mean insulin dose increases of 6% ICR (−64% to +29%), 6% ICR (−16% to +18%) and 21% ICR (−28% to +34%), respectively.

#### 3.3.3 | Food Insulin Index

The Food Insulin Index is an algorithm for ranking foods based on the 2-h postprandial insulin response to 1000 kJ portions in healthy adults. The clinical efficacy of this algorithm in managing glycaemia following fat and protein meals compared with carbohydrate counting was evaluated in two studies with discrepant results. Bell et al. reported that the Food Insulin Index resulted in significantly lower mean glucose (5.7 vs. 6.5 mmol/L, p = 0.003) over 3 h. However, both the Food Insulin Index and carbohydrate counting resulted in high rates of hypoglycaemia (48% vs. 33%). Lopez et al. found no significant difference in mean glucose excursions at
any 0.5 h interval over 5 h and no significant increase in the odds of hypoglycaemia \((p = 0.172)\).^{25}

3.3.4 | Pankowska Equation

Four studies, one in MDI therapy gave additional insulin for fat and protein meals using the Pankowska Equation.\(^5,19,23,25\) This equation postulates that the insulin required for 10 g (40 kcal) of carbohydrate (1 carbohydrate unit, CU) is equivalent to the insulin required for 100 kcal of fat (11 g) and/or protein (25 g) (1 fat-protein unit, FPU).\(^30\) Compared with carbohydrate counting, all four studies reported that the Pankowska Equation lowered postprandial glucose; however, in the three studies conducted in IPT, this was accompanied by increased rates of hypoglycaemia. Pankowska et al. reported significantly lower mean glucose excursions from 1 to 6 h \((p < 0.004)\) and a 25% increase \((4/12 \text{ vs. } 0/11)\) in the rate of hypoglycaemia.\(^5\) Kordonouri et al. found a significant reduction in the 6-h AUC \((784 \pm 235 \text{ vs. } 953 \pm 299 \text{ mg/dl}, p < 0.001)\) and a 26% increase in the rate of hypoglycaemia \([35.7\% \text{ vs. } 9.5\%, p < 0.001]\).\(^19\) Likewise, Lopez et al. reported a significant increase in time spent in the glucose target range \([+13.6\% (95\%CI; 2.3, 24.8), p = 0.018]\) and the odds of hypoglycaemia \([OR = 0.76, p < 0.001 \text{ (higher fat: } 7\% \text{ vs. } 45\%, \text{ higher protein: } 4\% \text{ vs. } 22\%)]\).\(^25\)

In MDI therapy, Kaya et al. found that the Pankowska Equation resulted in significantly lower mean postprandial glucose excursions from 2 h \((11.3 \text{ vs. } 13.3 \text{ mmol/L}, p = 0.011)\) to 4 h \((7.5 \text{ vs. } 11.0 \text{ mmol/L}, p < 0.001)\), with no incidence of hypoglycaemia over 4 h.\(^23\)

3.3.5 | Predetermined insulin dose increase

Three studies, two in MDI therapy gave additional insulin for fat and protein meals using a predetermined dose increase.\(^21,26,28\) In a comparison of four insulin doses, 100%, 120%, 140% and 160% ICR, Smith et al. reported that compared with 100% ICR, 140% and 160% ICR resulted in significantly lower 6-h AUCs \((822 \text{ and } 567 \text{ vs. } 1249 \text{ mmol/L/min, } p \leq 0.001)\) with no significant increase in the odds of hypoglycaemia \([OR = 1.56, p = 0.56 \text{ and } OR = 2.9, p = 0.14, \text{ respectively}]\).\(^26\) In MDI therapy, Campbell et al. found that bolus insulin dictated by carbohydrate, with an additional 30% resulted in lower mean postprandial glucose excursions from 2 to 6 h and a 60% increase in the rate of hypoglycaemia \((6/10)\).\(^21\) In contrast, Smith et al. demonstrated that the 5-h iAUC was significantly lower \((620 \text{ vs. } 341 \text{ mmol/L/min, } p = 0.016)\) following the administration of an additional 25% of the ICR with no incidence of hypoglycaemia.\(^28\)

3.3.6 | Manual correction boluses

van Der Hoogt et al. measured the amount of correction insulin required to manage glycaemia over 10 h and found that the addition of 7 g of fat and 16 g of protein to a control meal required a mean 31% increase in the total meal insulin dose \((3.5 \text{ U vs. } 2.7 \text{ U}, p < 0.001)\).\(^24\)

3.4 | Pattern of insulin delivery

Six studies examined the effect of altering the pattern of meal insulin delivery on glucose levels following fat and protein meals in people using IPT.\(^5,16,19,20,22,27\) Four studies reported reductions in mean glucose when using combination compared with standard boluses.\(^5,19,20,27\) One of these studies also reported reductions when using combination compared with split and extended boluses.\(^20\) The remaining two studies reported no improvement in glycaemic outcomes when using combination and extended boluses compared with standard boluses.\(^16,22\)

In a comparison of four bolus types; standard, split (50:50, 1.5 h), extended (2 h) and combination (70:30, 2 h) Chase et al. found that a combination bolus resulted in the lowest mean change in glucose from baseline at 2-h post-meal \([-0.4 \text{ vs. } 2.1 \text{ (standard) vs. } 3.3 \text{ (split) vs. } 3.8 \text{ mmol/L (extended), } p = 0.009]\).\(^20\) In contrast, Lopez et al. reported the AUC was significantly lower when using a combination \((30:70, 2 \text{ h})\) compared with a standard bolus \((36.8 \pm 5.0 \text{ vs. } 51.2 \pm 5.3 \text{ mmol/L/min, } p = 0.004)\) in the late postprandial period \((4–5 \text{ h})\), whereas Pankowska et al. reported significantly lower mean glucose excursions from 1 to 6 h \((p < 0.004)\) and Kordonouri et al. a significant reduction in 6-h AUC \((784 \pm 235 \text{ vs. } 953 \pm 299 \text{ mg/dl, } p < 0.001)\) when using combination \((70:30, 3 \text{ h})\) compared with standard boluses. However, it should be noted that both Pankowska et al. and Kordonouri et al. gave additional meal insulin in the combination boluses only which may have contributed to the increased efficacy.\(^5,19\) In contrast, De Palma et al. found no significant difference in the 6-h AUC when insulin was given as a combination bolus \((30:70, 6 \text{ h})\) compared with a standard bolus \(15 \text{ min before the meal}^{22}\) Similarly, Lindholm et al. found no significant difference in time to peak glucose, peak glucose or area under the glucose curve when using combination \((60:40 \text{ h})\), or extended \((1 \text{ h})\) boluses compared with standard boluses.\(^16\) However, consistent with Chase et al. the mean change in glucose between 0 and 1 h was significantly greater for the lower fat meal when using extended bolus \((1 \text{ h})\) \([4.6 \pm 2.8 \text{ vs. } 2.8 \pm 1.7 \text{ mmol/L, } p = 0.018]\).\(^16\)

Two studies evaluated the efficacy of a split insulin dose compared with a standard dose for fat and protein meals in MDI therapy.\(^21,28\) Campbell et al. reported high rates of hypoglycaemia \((60\%)\) following preprandial administration of
130% ICR compared with delivering the additional meal insulin (30% ICR) in a second injection, 3 h post-meal. In contrast, Smith et al. found no significant difference in the 5-h iAUC when 125% ICR was given in a standard dose versus a split dose (100:25, 1 h) (341 vs. 434 mmol/L.min, \( p = 0.900 \)) with no incidence of hypoglycaemia under either condition.\(^{28} \)

### 3.5 | Insulin dose split

Three studies investigated the optimal split of meal insulin in a combination bolus for a high-fat, high-protein meal and a range of high-fat meals in people using IPT.\(^{13,15,27} \) Two of these studies also reported the optimal mean duration of the extended bolus component.\(^{13,15} \)

In a comparison of five different combination bolus split conditions (30–70:70–30, 2 h) Lopez et al. found that for a high-fat, high-protein meal, the AUC was significantly lower than 2 h when using standard (39.7 mmol/L/min) compared with combination bolus 40:60 (50.7 mmol/L/min, \( p = 0.02 \)) and 50:50 (65.7 mmol/L/min \( p = 0.025 \)).\(^{27} \) The investigators concluded that a minimum of 60% ICR is required in the standard bolus component of a combination bolus to adequately control the early postprandial glucose rise (0–2 h).\(^{27} \) In contrast, Bell et al. reported that for a high-fat, high-protein meal, a mean combination bolus split of 30:70 and a mean duration of 2.4 h was optimal (range 2–3 h).\(^{15} \) Given the dose was increased on average by 65% of the ICR (8 out of 10 participants required +75% to 124% ICR), when split 30:70, this translates to an average upfront insulin dose equivalent to 50% of the ICR (8 out of 10 participants required 53%–67% ICR). Furthermore, Bell et al. demonstrated that as the fat content of a fixed carbohydrate and protein meal was incrementally increased the mean optimal upfront insulin requirement successively decreased (+20 g = 78% ICR, +40 g = 67% ICR, +60 g = 60% ICR) while the mean optimal duration of the extended bolus was successively longer (+20 g = 1.2 h, +40 g = 1.3 h, +60 g = 1.8 h).\(^{13} \)

A further two studies examined the optimal insulin dose split for fat and protein meals in people using MDI therapy.\(^{21,28} \) Campbell et al. reported no incidence of hypoglycaemia over 6 h following the preprandial administration of 100% ICR (100:0, 100:30, 3 h) yet, increasing the upfront dose to 130% ICR (130:0) resulted in a 60% increase in the rate of hypoglycaemia.\(^{21} \) In contrast, Smith et al. found that increasing the upfront insulin dose from 100% to 125% ICR significantly lowered the mean postprandial glucose peak (4.1 vs. 3.1 mmol/L, \( p = 0.044 \)) and mean postprandial glucose excursions from 1 h (1.5 vs. 0.5 mmol/L, \( p = 0.001 \)) to 4.5 h (2.1 vs. 0.9 mmol/L, \( p = 0.043 \)) with no incidence of hypoglycaemia over 5 h.\(^{21} \)

### 3.6 | Timing of insulin delivery

Two studies investigated the timing of meal insulin delivery relative to meal consumption.\(^{22,29} \) Thuillier et al. demonstrated significantly lower mean postprandial glucose excursions at 1 h (\( p = 0.04 \)) and 2 h (\( p = 0.02 \)) when insulin was delivered 15 min prior to, rather than immediately after a high-fat meal. This was accompanied by a twofold increase in the rate of postprandial hypoglycaemia \([n = 33%^{7} vs. 14%^{7}] \) over 4 h.\(^{29} \) Similarly, for a pizza margherita meal, De Palma et al. reported a lower 6-h AUC when insulin was given 15 min prior to, rather than immediately prior to the meal \((6.9 \pm 14.9 vs. 4.2 \pm 25.9 \text{ mg/dl/min}^{10^{5}} \)). Mild hypoglycaemia (capillary glucose <80 mg/dl or 4.4 mmol/L) was noted in some participants; however, the number of episodes under each condition were not reported.\(^{22} \)

### 3.7 | Quality assessment

The risk of bias in the included studies is shown in Figure 2. Although all studies carried some risk of bias according to the Cochrane Risk of Bias Assessment Tool overall, the quality of studies was high. As per the inclusion criteria, all studies were randomised controlled trials. The majority of studies adequately described a method of random sequence generation (10 out of 18)\(^{5,13,14,20,22,25–29} \) deemed to be at low risk for selection bias yet, very few studies (3 out of 18) stated whether the intervention allocation was concealed from participants and personnel enrolling participants.\(^{5,14,22} \) Most studies (12 out of 18) used intention-to-treat analyses with participant drop-out and missing data balanced across groups\(^{5,14–17,19,22,26–29} \) the risk for attrition bias across these studies was determined to be low. Three studies were identified as having a high risk of attrition bias,\(^{13,18,24} \) these studies used per protocol analyses, which excluded a large proportion (≥25%) of the total data collected. The majority of studies (14 out of 18) pre-specified outcomes and adequately reported on these outcomes and overall, reporting bias was deemed to be low.\(^{5,13–19,22,24,26–29} \) All studies were considered to be free of performance and detection biases. Of the 18 included studies, only two studies reported blinding of participants and personnel to the intervention allocation\(^{14,17} \) and none reported blinding of outcome assessors. However, the nature of the intervention (test meal) meant that blinding was not possible in the majority of studies (11 out of 18)\(^{13–18,21,23–25,29} \) and when coupled with the use of objective outcome measures such as capillary and plasma blood glucose testing it was determined that a lack of blinding of participants, personnel and outcome assessors was not likely to influence study outcomes. Other sources of bias originated from a small sample size (pilot) and failure to report the sample size calculation.\(^{14,15,17,18,20–22,24} \)
The present review identified four strategies for managing the glycaemic impact of mixed meals, the majority of which contained ≥30 g carbohydrate with fat and protein, including increasing the insulin dose, altering the pattern of insulin delivery, adjusting the insulin dose split and varying the timing of insulin delivery. Giving additional insulin for dietary fat and protein was the most common strategy identified. Of the five studies that gave additional insulin for fat and fat and protein added to control meals,17,18,21,23,24 three reported that a mean dose increase of 30%–43% ICR was required for the addition of 32–50 g of fat, such that the meals contained a total of 33–60 g of fat17,18,21 and the addition of 35 g of fat with 27 g of protein, such that the meal contained a total of 36 g of fat with 34 g of protein.17 The remaining two studies reported that a proportionately higher-dose increase of 31%24 and 50% ICR23 was necessary for just 7 g of added fat with 16 g of added protein (total fat 15 g and protein 27 g) and 13 g of added fat with 12 g of added protein (total fat 30 g and protein 36 g), respectively. In one study,24 the prolonged suspension of basal insulin delivery following the low-fat, low-protein control meal (86 ± 80 vs. 53 ± 54 min, \( p = 0.052 \)) compared with the high-fat, high-protein meal and in the other study,23 failure to optimise the ICR may have led to the overestimation of additional insulin needs.

A further eight studies calculated additional insulin for dietary fat and protein using alternate dosing algorithms. For meals containing ≥19 g carbohydrate with 2–79 g of fat and 10–50 g of protein, the mean additional insulin provided ranged from 3% to 75% ICR, with only one study reporting a glycaemic benefit of giving less than an additional 24% ICR.13 In this study, it is possible that a high habitual fat intake among participants relative to the test meal composition may have led to an overestimation of the ICR and underestimation of additional insulin needs. This is supported by findings of a high rate of...
hypoglycaemia (47%) following the no fat control meal with identical carbohydrate content. Only one study reported giving insulin for a meal containing fat (11 g) and protein (60 g), a high rate (75%) of postprandial hypoglycaemia was reported. This is consistent with the previous findings of Paterson et al. which suggests that only very large protein loads of >75 g consumed in isolation may require insulin. Overall, no superior method of insulin dose calculation for fat and protein was identified. The Pankowska Equation and the Food Insulin Index were associated with increased rates of hypoglycaemia (21%–75%), whereas studies using proportional integral derivative control and model predictive bolus algorithms reported large, inter-individual variation in additional insulin needs (−64% to +124% ICR).

In addition to insulin amount, the timing and pattern of insulin delivery is a key determinant of the effectiveness of the insulin strategy. Consistent with previous studies, findings support preprandial insulin dosing for fat and protein meals; however, for very-high-fat meals (>60 g), there may be an increased risk of hypoglycaemia. In IPT, two of two studies agreed that extended boluses were unable to manage the early rise in postprandial glucose following fat and protein meals. Four of six studies reported significant reductions in postprandial glucose when using combination compared with standard boluses; however, half of these studies gave additional insulin in the combination bolus only. The two studies that reported no glycaemic benefit of using combination over standard bolus had test meals with the lowest fat content. Furthermore, one study gave an upfront insulin dose of just 30% ICR and in the other, the postprandial glucose monitoring period was just 3 h in duration.

In MDI therapy, there is very little evidence to guide insulin delivery for fat and fat and protein meals. The current review identified only two studies both investigated the clinical efficacy of a split insulin dose strategy with discrepant findings. Where Campbell et al. described increased rates of hypoglycaemia following preprandial administration of 130% ICR for a meal containing 68 g of carbohydrate, 55 g of fat and 26 g of protein that was resolved by giving the additional meal insulin in a second injection 3 h post-meal. Smith et al. found no incidence of hypoglycaemia following the preprandial administration of 125% ICR for a meal containing 30 g of carbohydrate, 40 g of fat and 50 g of protein and no additional glycaemic benefit of giving additional meal insulin in a second injection, 1 h post-meal. Furthermore, larger studies in well controlled groups using MDI therapy testing a range of insulin dose splits for meals with varying fat and protein content are required.

The addition of fat and protein to meals has been shown to significantly delay, although increase the early postprandial glucose rise. In practice, this presents challenges for people living with type 1 diabetes who must balance the need for sufficient upfront insulin with minimising the risk of early postprandial hypoglycaemia. In the present review, despite differences in test meal macronutrient composition (carbohydrate: 30–50 g, fat: 22–62 g, protein: 2–40 g) and research methodology, the majority of studies investigating the optimal split of meal insulin for fat and fat and protein meals reported a mean upfront insulin requirement of at least 60% ICR and where applicable, an extended bolus duration of 1–3 h was necessary. For fat meals containing minimal protein (<15 g), there was a trend towards decreasing upfront insulin requirement (78%–60% ICR) with increasing fat content while for fat meals containing ≥25 g protein an upfront insulin dose of 70%–125% ICR was well tolerated.

There were some important methodological limitations of the included studies. Studies were small, with eight (out of 18) studies having <20 participants. Two studies limited the postprandial monitoring period to just 3 h, these studies may have failed to capture the late, sustained glycaemic impact of fat and protein commencing from 3 h. Six studies adjusted insulin from 0.5 to 2.5 h prior to meal delivery or with the test meal to meet study day eligibility criteria. Two of these studies also suspended basal insulin during the monitoring period to prevent hypoglycaemia. Given that the duration of action of rapid-acting insulin is 3–5 h, this may have resulted in differences in the amount of active insulin on-board across study days.

4.1 Clinical implications

• Overall, for fat and fat and protein meals with at least 19 g carbohydrate findings support recommendations for a minimum starting insulin dose increase equivalent to 24% ICR increasing up to a maximum of 75% ICR with titration based on the individual postprandial glycaemic response. Where continuous glucose monitoring is not available postprandial capillary blood glucose testing at 1.5, 3 and 6 h is recommended.

• Findings of studies investigating the additional insulin dose needed for fat and fat and protein added to control meals (n = 5) support an insulin dose increase of 30% ICR for carbohydrate meals with >30 g of fat or >15 g of fat with >25 g of protein.

• In MDI therapy, the research is equivocal regarding splitting the insulin dose.

• In IPT, there is evidence to support the use of combination but not extended boluses over standard boluses. An upfront dose of 70% ICR delivered 15 min prior to the meal is advised, with the duration of the extended bolus set between 1 and 3 h.

• The percentage of insulin delivered upfront is likely to differ depending on the individual sensitivity to fat and
protein and the total meal composition; meals with a higher fat content relative to protein may require less upfront insulin (50%–<70% ICR), whereas those with a higher protein content relative to fat may require more upfront insulin (>70%–125% ICR).

4.1.1 | Clinical considerations

In practice, prior to adjusting the meal insulin strategy, it is important to address other potential causes of postprandial hyperglycaemia, including inaccuracies in carbohydrate counting, missed meal insulin doses, postprandial dosing, additional intake of food or drink as well as inaccuracies in the ICR and/or the basal insulin dose. Furthermore, given the increased incidence of obesity33,34 and risk of vascular complications35,36 in this population, adjusting the insulin strategy for fat and fat and protein meals should always be discussed in the context of a healthy diet with individualized guidance around appropriate energy intake and physical activity.

In conclusion, these findings highlight the potential glycaemic benefits of considering meal fat and protein when determining the insulin dosing and delivery strategy but also the added complexity and burden that is likely to accompany such adjustments. The authors acknowledge that adjusting insulin to carbohydrate alone can be challenging, and that implementation of these findings into clinical care may only be possible with the introduction of novel decision making support tools.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

T.A.S. developed the search strategy; screened papers for review; extracted data; conducted the risk of bias assessment and wrote the manuscript. A.A.M. developed the search strategy; screened papers for review and conducted the risk of bias assessment. B.R.K. contributed to writing the manuscript. C.E.S. developed the search strategy; screened papers for review and contributed to writing the manuscript. All authors reviewed the final manuscript.

ORCID

Tenele A. Smith © https://orcid.org/0000-0002-9403-4679
Bruce R. King © https://orcid.org/0000-0002-8958-7404
Carmel E. Smart © https://orcid.org/0000-0003-3104-8800

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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