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Interventions for people with type 2 diabetes mellitus fasting during Ramadan (Review)

Lee SWH, Chen WS, Sellappans R, Md.Sharif SB, Metzendorf MI, Lai NM

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[Intervention Review]

Interventions for people with type 2 diabetes mellitus fasting during Ramadan

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ABSTRACT

Background

Fasting during Ramadan is obligatory for adult Muslims, except those who have a medical illness. Many Muslims with type 2 diabetes (T2DM) choose to fast, which may increase their risks of hypoglycaemia and dehydration.

Objectives

To assess the effects of interventions for people with type 2 diabetes fasting during Ramadan.

Search methods

We searched CENTRAL, MEDLINE, PsycINFO, CINAHL, WHO ICTRP and ClinicalTrials.gov (29 June 2022) without language restrictions.

Selection criteria

Randomised controlled trials (RCTs) conducted during Ramadan that evaluated all pharmacological or behavioural interventions in Muslims with T2DM.

Data collection and analysis

Two authors screened and selected records, assessed risk of bias and extracted data independently. Discrepancies were resolved by a third author. For meta-analyses we used a random-effects model, with risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes with their associated 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach.

Main results

We included 17 RCTs with 5359 participants, with a four-week study duration and at least four weeks of follow-up. All studies had at least one high-risk domain in the risk of bias assessment.

Four trials compared dipeptidyl-peptidase-4 (DPP-4) inhibitors with sulphonylurea. DPP-4 inhibitors may reduce hypoglycaemia compared to sulphonylureas (85/1237 versus 165/1258, RR 0.53, 95% CI 0.41 to 0.68; low-certainty evidence). Serious hypoglycaemia was similar between groups (no events were reported in two trials; 6/279 in the DPP-4 versus 4/278 in the sulphonylurea group was reported in one

trial, RR 1.49, 95% CI 0.43 to 5.24; very low-certainty evidence). The evidence was very uncertain about the effects of DPP-4 inhibitors on adverse events other than hypoglycaemia (141/1207 versus 157/1219, RR 0.90, 95% CI 0.52 to 1.54) and HbA1c changes (MD -0.11%, 95% CI -0.57 to 0.36) (very low-certainty evidence for both outcomes). No deaths were reported (moderate-certainty evidence). Health-related quality of life (HRQoL) and treatment satisfaction were not evaluated.

Two trials compared meglitinides with sulphonylurea. The evidence is very uncertain about the effect on hypoglycaemia (14/133 versus 21/140, RR 0.72, 95% CI 0.40 to 1.28) and HbA1c changes (MD 0.38%, 95% CI 0.35% to 0.41%) (very low-certainty evidence for both outcomes). Death, serious hypoglycaemic events, adverse events, treatment satisfaction and HRQoL were not evaluated.

One trial compared sodium-glucose co-transporter-2 (SGLT-2) inhibitors with sulphonylurea. SGLT-2 may reduce hypoglycaemia compared to sulphonylurea (4/58 versus 13/52, RR 0.28, 95% CI 0.10 to 0.79; low-certainty evidence). The evidence was very uncertain for serious hypoglycaemia (one event reported in both groups, RR 0.90, 95% CI 0.06 to 13.97) and adverse events other than hypoglycaemia (20/58 versus 18/52, RR 1.00, 95% CI 0.60 to 1.67) (very low-certainty evidence for both outcomes). SGLT-2 inhibitors result in little or no difference in HbA1c (MD 0.27%, 95% CI -0.04 to 0.58; 1 trial, 110 participants; low-certainty evidence). Death, treatment satisfaction and HRQoL were not evaluated.

Three trials compared glucagon-like peptide 1 (GLP-1) analogues with sulphonylurea. GLP-1 analogues may reduce hypoglycaemia compared to sulphonylurea (20/291 versus 48/305, RR 0.45, 95% CI 0.28 to 0.74; low-certainty evidence). The evidence was very uncertain for serious hypoglycaemia (0/91 versus 1/91, RR 0.33, 95% CI 0.01 to 7.99; very low-certainty evidence). The evidence suggests that GLP-1 analogues result in little to no difference in adverse events other than hypoglycaemia (78/244 versus 55/255, RR 1.50, 95% CI 0.86 to 2.61; very low-certainty evidence), treatment satisfaction (MD -0.18, 95% CI -3.18 to 2.82; very low-certainty evidence) or change in HbA1c (MD -0.04%, 95% CI -0.45% to 0.36%; 2 trials, 246 participants; low-certainty evidence). Death and HRQoL were not evaluated.

Two trials compared insulin analogues with biphasic insulin. The evidence was very uncertain about the effects of insulin analogues on hypoglycaemia (47/256 versus 81/244, RR 0.43, 95% CI 0.13 to 1.40) and serious hypoglycaemia (4/131 versus 3/132, RR 1.34, 95% CI 0.31 to 5.89) (very low-certainty evidence for both outcomes). The evidence was very uncertain for the effect of insulin analogues on adverse effects other than hypoglycaemia (109/256 versus 114/244, RR 0.83, 95% CI 0.44 to 1.56; very low-certainty evidence), all-cause mortality (1/131 versus 0/132, RR 3.02, 95% CI 0.12 to 73.53; very low-certainty evidence) and HbA1c changes (MD 0.03%, 95% CI -0.17% to 0.23%; 1 trial, 245 participants; very low-certainty evidence). Treatment satisfaction and HRQoL were not evaluated.

Two trials compared telemedicine with usual care. The evidence was very uncertain about the effect of telemedicine on hypoglycaemia compared with usual care (9/63 versus 23/58, RR 0.42, 95% CI 0.24 to 0.74; very low-certainty evidence), HRQoL (MD 0.06, 95% CI -0.03 to 0.15; very low-certainty evidence) and HbA1c change (MD -0.84%, 95% CI -1.51% to -0.17%; very low-certainty evidence). Death, serious hypoglycaemia, AEs other than hypoglycaemia and treatment satisfaction were not evaluated.

Two trials compared Ramadan-focused patient education with usual care. The evidence was very uncertain about the effect of Ramadan-focused patient education on hypoglycaemia (49/213 versus 42/209, RR 1.17, 95% CI 0.82 to 1.66; very low-certainty evidence) and HbA1c change (MD -0.40%, 95% CI -0.73% to -0.06%; very low-certainty evidence). Death, serious hypoglycaemia, adverse events other than hypoglycaemia, treatment satisfaction and HRQoL were not evaluated.

One trial compared drug dosage reduction with usual care. The evidence is very uncertain about the effect of drug dosage reduction on hypoglycaemia (19/452 versus 52/226, RR 0.18, 95% CI 0.11 to 0.30; very low-certainty evidence). No participants experienced adverse events other than hypoglycaemia during the study (very low-certainty evidence). Death, serious hypoglycaemia, treatment satisfaction, HbA1c change and HRQoL were not evaluated.

Authors' conclusions

There is no clear evidence of the benefits or harms of interventions for individuals with T2DM who fast during Ramadan. All results should be interpreted with caution due to concerns about risk of bias, imprecision and inconsistency between studies, which give rise to low- to very low-certainty evidence. Major outcomes, such as mortality, health-related quality of life and severe hypoglycaemia, were rarely evaluated. Sufficiently powered studies that examine the effects of various interventions on these outcomes are needed.

PLAIN LANGUAGE SUMMARY

Interventions for people with type 2 diabetes mellitus fasting during Ramadan

Review question

What are the effects of interventions for adults with type 2 diabetes who fast during Ramadan?

Background

Fasting during Ramadan is one of the pillars of Islam's core beliefs and practices. During this period, all healthy Muslim adults will fast from dawn to dusk (sunset) and take meals after sunset or Iftar. People who are ill or have medical conditions such as type 2 diabetes are exempted from fasting. However, many individuals with type 2 diabetes choose to fast during Ramadan, which can have a major impact

on managing diabetes in the Muslim population. Due to the metabolic nature of the condition, people with diabetes are at particular risk of complications from marked changes in food and liquid intake, including the risk of hypoglycaemia.

We wanted to find out the effects of interventions used to support fasting in adults with type 2 diabetes during Ramadan. We were specifically interested in the effects on hypoglycaemia (both non-serious and serious), quality of life and unwanted events. We included studies on adults with type 2 diabetes, and our search date was 29 June 2022.

Study characteristics

We found 17 studies with a total of 5359 participants. These studies were conducted for at least four weeks during Ramadan, and participants were followed up for at least four weeks. The included studies compared the use of sulphonylureas with the use of dipeptidyl peptidase-4 inhibitors (four studies), meglitinides (two studies), sodium-glucose co-transporter-2 inhibitors (one study) and glucagon-like peptide-1 analogues (three studies) during Ramadan. Two studies compared insulin analogues with biphasic insulin. Other studies compared usual care with telemedicine (two studies), Ramadan-focused patient education (two studies) and a reduction in drug dosage during Ramadan (one study).

Key results

Data were sparse for all comparisons. The available data did not show any clear benefit or harm of either pharmacological or behavioural interventions to support people with type 2 diabetes who wish to fast during Ramadan. However, evidence from studies suggests that using antidiabetic drugs other than sulfonylurea may reduce the risk of experiencing hypoglycaemia. Similarly, behavioural interventions such as telemedicine (providing treatment advice remotely) or reducing the dose of diabetes medications during Ramadan may reduce the risk of experiencing hypoglycaemia. In studies reporting severe hypoglycaemic episodes, events were rare, with similarly low numbers across all comparisons. Information on health-related quality of life and all-cause mortality was scarce yet did not suggest apparent differences between all interventions. Moreover, the few available data did not indicate apparent differences between pharmacological and behavioural interventions regarding the risk of experiencing adverse events other than hypoglycaemia, blood pressure, body weight, lipid levels or glycated haemoglobin levels.

Certainty of the evidence

For all the studies in this review, there are concerns about the methodological quality and the subsequent certainty of evidence. The number of participants in all interventions was small. For the reported outcomes, we have very little confidence in the certainty of the available evidence. Future studies may substantially change our findings.

Summary of findings 1. DPP-4 inhibitors versus sulphonylureas

DPP-4 inhibitors compared to sulphonylureas for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: DPP-4 inhibitors with or without metformin
Comparison: second and third generation sulphonylureas (glimepiride, gliclazide, glibenclamide) with or without metformin

Outcomes	Risk with sulphonylureas	Risk with DPP-4 inhibitors	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 12 weeks b) Serious hypoglycaemia (defined as hypoglycaemic events requiring assistance) Follow-up: 4 to 12 weeks	(a) **131 per 1000** (b) **22 per 1000**	(a) **70 per 1000** (54 to 89) (b) **32 per 1000** (9 to 113)	(a) **RR 0.53** (0.41 to 0.68) b) **RR 1.49** (0.43 to 5.24)	a) 2495 (4) b) 2426 (3)	(a) ⊕⊕⊖⊖ **low**[a] (b) ⊕⊖⊖⊖ **very low**[b]	(b) The pooled relative effect is based on only one study; the other two studies could not be included as they reported zero events in both intervention and control groups.
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia Follow-up: 4 to 12 weeks	**129 per 1000**	**116 per 1000** (67 to 198)	**RR 0.90** (0.52 to 1.54)	2426 (3)	⊕⊖⊖⊖ **very low**[c]	—
All-cause mortality Follow-up: 4 to 12 weeks	See comment			2426 (3)	⊕⊕⊕⊖ **moderate**[d]	All three studies reported zero deaths in both intervention and control groups.
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: 4 to 12 weeks	The mean HbA1c ranged across the sulphonylurea group	The mean HbA1c in the **DPP-4 groupswas0.1% lower** (0.6% lower to 0.4% higher) compared to	—	626 (2)	⊕⊖⊖⊖ **very low**[e]	—

	from**6.8% to7.5%**	the sulphonylurea groups				
Self-care	**Not reported**					—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DPP-4**: dipeptidyl-peptidase 4; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level because of risk of bias (detection bias) and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (detection bias), and by two levels because of serious imprecision (small number of studies; wide CI that includes both benefit and harm).
[c]Downgraded by one level because of risk of bias (detection bias), by one level because of inconsistency (the non-consistent direction of effects) and by one level because of imprecision (small number of studies).
[d]Downgraded by one level because of imprecision (insufficient duration to detect outcome).
[e]Downgraded by one level because of inconsistency (non-consistent direction of effects) and by two levels because of serious imprecision (small number of studies; CI consistent with benefit and harm).

Summary of findings 2. Meglitinides versus sulphonylureas

Meglitinides compared to sulphonylureas for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: meglitinides with or without metformin
Comparison: second and third generation sulphonylureas (glimepiride, gliclazide, glibenclamide) with or without metformin

Outcomes	Risk with sulphonylureas	Risk with meglitinides	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 14 weeks	(a)**150 per 1000** (b) **Not reported**	(a)**108 per 1000** (60 to 192) (b) **Not reported**	(a) **RR 0.72** (0.40 to 1.28) (b) **Not reported**	(a) 273 (2) (b) **Not reported**	(a) ⊕⊖⊖⊖ **very low**[a] (b) **Not reported**	(b) No studies reported on serious hypoglycaemia

b) Serious hypoglycaemia (defined as hypoglycaemic events requiring assistance)						
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia	**Not reported**					—
All-cause mortality	**Not reported**					—
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: week 14	The mean HbA1c in the sulphonylurea group was 7.8%	The mean HbA1c in the meglitinide group was **0.38% higher** (0.35% higher to 0.41% higher)	—	235 (1)	⊕⊖⊖⊖ **very low**[b]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level because of risk of bias (detection bias) and by two levels because of serious imprecision (small number of studies; CI consistent with benefit and harm).
[b]Downgraded by one level because of indirectness (insufficient time frame) and by two levels because of serious imprecision (small number of studies; CI includes both benefit and harm).

Summary of findings 3. SGLT-2 inhibitors versus sulphonylureas

SGLT-2 inhibitors compared to sulphonylureas for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: SGLT-2 inhibitors with or without metformin
Comparison: second and third generation sulphonylureas (glimepiride, gliclazide, glibenclamide) with or without metformin

Outcomes	Risk with sulphonylureas	Risk with SGLT-2 inhibitors	Relative effect (95% CI)	No of participants	Certainty of the evidence	Comments

				(studies)	(GRADE)	
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 12 weeks b) Serious hypoglycaemia (not defined) Follow-up: 4 to 12 weeks	(a) **250 per 1000** (b) **19 per 1000**	(a) **150 per 1000** (25 to 198) (b) **17 per 1000** (1 to 269)	(a) **RR 0.28** (0.10 to 0.79) b) **RR 0.90** (0.06 to 13.37)	a) 110 (1) b) 110 (1)	(a) ⊕⊕⊖⊖ **low**[a] (b) ⊕⊖⊖⊖ **very low**[b]	—
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia Follow-up: 4 to 12 weeks	**346 per 1000**	**346 per 1000** (208 to 578)	**RR 1.00** (0.60 to 1.67)	110 (1)	⊕⊖⊖⊖ **very low**[c]	—
All-cause mortality	**Not reported**					—
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: 12 weeks	The mean HbA1c in the sulphonylurea groups was 7.3%	The mean HbA1c in the SGLT-2 groups was **0.27% higher** (0.04% lower to 0.58% higher)	—	103 (1)	⊕⊕⊖⊖ **low**[d]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **SGLT-2**: sodium glucose co-transporter-2; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level because of risk of bias (detection bias) and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (detection bias) and by two levels because of serious imprecision (small number of studies; CI consistent with benefit and harm).
[c]Downgraded by two levels because of serious imprecision (small number of studies; CI includes both benefit and harm) and by one level because of indirectness (insufficient time frame).
[d]Downgraded by two levels because of serious imprecision (small number of studies; CI includes both benefit and harm).

Summary of findings 4. GLP-1 analogues inhibitors versus sulphonylureas

GLP-1 analogues compared to sulphonylureas for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: GLP-1 analogues with or without metformin
Comparison: second and third generation sulphonylureas (glimepiride, gliclazide, glibenclamide) with or without metformin

Outcomes	Risk with sulphonylureas	Risk with GLP-1 analogues	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 12 weeks b) Serious hypoglycaemia (defined as hypoglycaemic events requiring assistance or plasma glucose value < 3.1 mmol/L) Follow-up: 4 to 12 weeks	(a) **157 per 1000** (b) **11 per 1000**	(a) **71 per 1000** (44 to 116) (b) **4 per 1000** (0 to 89)	(a) **RR 0.45** (0.28 to 0.74) b) **RR 0.33** (0.01 to 7.99)	a) 596 (3) b) 596 (3)	(a) ⊕⊕⊖⊖ **low**[a] (b) ⊕⊖⊖⊖ **very low**[b]	(b) The pooled relative effect is based on only one study; two studies could not be included as they reported zero events in both intervention and control groups.
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia Follow-up: 4 to 12 weeks	**216 per 1000**	**324 per 1000** (185 to 563)	**RR 1.50** (0.86 to 2.61)	499 (3)	⊕⊖⊖⊖ **very low**[c]	—
All-cause mortality	**Not reported**					—
Treatment satisfaction	The mean treatment satisfaction score in the sulphonylurea group was 30.51 points	The mean treatment satisfaction score in the GLP analogue group was **0.18 lower** (3.18 lower to 2.82 higher)	—	62 (1)	⊕⊖⊖⊖ **very low**[d]	—
HbA1c (%) Follow-up: 12 to 24 weeks	The mean HbA1c ranged across the sulphonylurea group from 7.8% to 8.0%	The mean HbA1c in the GLP analogue group was **0.04% lower** (0.45% lower to 0.36% higher)	—	246(2)	⊕⊕⊖⊖ **low**[e]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **GLP-1:** glucagon-like peptide-1; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level because of risk of bias (detection bias) and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (detection bias) and by two levels because of serious imprecision (small number of studies and wide CI, which includes both benefit and harm).
[c]Downgraded by one level because of risk of bias (detection bias) and by two levels because of serious imprecision (small number of studies; CI which includes both benefit and harm).
[d]Downgraded by two levels because of risk of bias (performance bias, detection bias) and by one level because of imprecision (small number of studies).
[e]Downgraded by two levels because of serious imprecision (small number of studies; CI which includes both benefit and harm).

Summary of findings 5. Insulin analogues versus biphasic insulin

Insulin analogues compared to biphasic insulin for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: insulin analogues (degludec or detemir)
Comparison: biphasic insulin (insulin aspart protamine and insulin aspart)

Outcomes	Risk with biphasic insulin	Risk with insulin analogues	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 12 weeks b) Serious hypoglycaemia (defined as hypoglycaemic events requiring assistance) Follow-up: 4 to 12 weeks	(a) **332 per 1000** (b) **23 per 1000**	(a) **143 per 1000** (43 to 465) (b) **30 per 1000** (7 to 134)	(a) **RR 0.43** (0.13 to 1.40) (b) **RR 1.34** (0.31 to 5.89)	a) 500 (2) b) 263 (1)	(a) ⊕⊖⊖⊖ **very low**[a] (b) ⊕⊖⊖⊖ **very low**[a]	—
Health-related quality of life	**Not reported**					—

Any adverse events other than hypoglycaemia Follow-up: 4 to 12 weeks	**467 per 1000**	**388 per 1000** (206 to729)	**RR 0.83** (0.44 to 1.56)	500 (2)	⊕⊖⊖⊖ **very low**[b]	—
All-cause mortality	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3.02** (0.12 to 73.53)	263 (1)	⊕⊖⊖⊖ **very low**[c]	Mortality was reported for 1/131 participants in the insulin analogue group and 1/132 participants in the biphasic insulin group.
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: end of Ramadan	The mean HbA1c in the biphasic insulin group was 8.2%	The mean HbA1c in the **insulin analogue group** was **0.03% higher** (0.2% lower to 0.2% higher)	—	245 (1)	⊕⊖⊖⊖ **very low**[d]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of risk of bias (performance bias, detection bias), and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (detection bias), and by two levels because of imprecision (small number of studies, CI includes benefit and harms).
[c]Downgraded by one level because of risk of bias (detection bias), and by two levels because of imprecision (small number of studies, wide confidence intervals).
[d]Downgraded by one level because of risk of bias (detection bias), and by two levels because of imprecision (small number of studies, CI includes benefit and harms).

Summary of findings 6. Telemedicine versus usual care

Telemedicine compared to usual care for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: remotely monitoring and advice of patients using telemedicine
Comparison: usual care (pharmacological treatment based upon national guidelines)

Outcomes	Risk with usual care	Risk with telemedicine	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes a) Non-serious hypoglycaemia Follow-up: 4 to 12 weeks b) Serious hypoglycaemia	(a)**397 per 1000** (b)**Not reported**	(a) **167 per 1000** (95 to 293) (b)**Not reported**	(a)**RR 0.42** (0.24 to 0.74) (b)**Not reported**	(a) 121 (2) (b)**Not reported**	⊕⊖⊖⊖ **very low**[a] (b)**Not reported**	(b) Neither study reported on serious hypoglycaemia.
Health-related quality of life Defined using: EQ-5D-3L (higher values represent better quality of life) Follow-up: end of study	The mean quality of life in the usual care group was 0.81 points	The mean quality of life in the **telemedicine group** was **0.06 points higher** (0.03 lower to 0.15 higher) compared to the usual care group	—	85 (1)	⊕⊖⊖⊖ **very low**[b]	—
Adverse events other than hypoglycaemia	**Not reported**					—
All-cause mortality	**Not reported**					—
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: end of Ramadan	The mean HbA1c in the usual care group was 8.3%	The mean HbA1c in the **telemedicine group** was **0.8% lower** (1.5% lower to 0.2% lower)	—	85 (1)	⊕⊖⊖⊖ **very low**[c]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of risk of bias (performance bias, detection bias), and by one level because of imprecision (small number of studies).
[b]Downgraded by one levels because of risk of bias (detection bias), and by two levels because of imprecision (small number of studies; CI includes both benefit and harm).
[c]Downgraded by two levels because of risk of bias (performance bias, detection bias), and by one level because of imprecision (small number of studies).

Summary of findings 7. Patient education versus usual care

Patient education compared to usual care for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: Ramadan-focused patient education
Comparison: usual care (pharmacological treatment based upon national guidelines)

Outcomes	Risk with usual care	Risk with patient education	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes (a) Non-serious hypoglycaemia Follow-up: 4 weeks (b) Serious hypoglycaemia	(a) **201 per 1000** (b)**Not reported**	(a) **235 per 1000** (165 to 334) (b)**Not reported**	(a) **RR 1.17** (0.82 to 1.66) (b)**Not reported**	(a) 377 (2) (b)**Not reported**	(a) ⊕⊖⊖⊖ **very low**[a] (b)**Not reported**	(b) No studies reported on this outcome
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia	**Not reported**					—
All-cause mortality	**Not reported**					—
Treatment satisfaction	**Not reported**					—
HbA1c (%) Follow-up: end of Ramadan	The mean HbA1c ranged across the usual care group from 7.7% to 14.0%	The mean HbA1c in the **patient education group** was **0.4% lower** (0.73% lower to 0.06% lower)	—	422 (2)	⊕⊖⊖⊖ **very low**[b]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by one level because of risk of bias (detection bias), by one level because of inconsistency (non-consistent direction of effects) and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (performance bias) and by two levels because of serious imprecision (small number of studies; wide CI).

Summary of findings 8. Drug dosage reduction versus usual care

Drug dosage adjustment compared to usual care for people with type 2 diabetes mellitus fasting during Ramadan

Patient: people with type 2 diabetes mellitus fasting during Ramadan
Setting: outpatients
Intervention: reduction of oral diabetes medication dosage during Ramadan
Comparison: usual care where dosage of oral diabetes medication is maintained

Outcomes	Risk with usual care	Risk with drug dosage adjustment	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Hypoglycaemic episodes (a) Non-serious hypoglycaemia Follow-up: 4 weeks (b) Serious hypoglycaemia	(a)**230 per 1000** (b)**Not reported**	(a) **41 per 1000** (25 to 69) (b)**Not reported**	(a) **RR 0.18** (0.11 to 0.30) (b)**Not reported**	(a) 678 (1) (b)**Not reported**	(a) ⊕⊖⊖⊖ **very low**[a] (b)**Not reported**	(b) No study reported on this outcome.
Health-related quality of life	**Not reported**					—
Adverse events other than hypoglycaemia	See comment	See comment	See comment	678 (1)	⊕⊖⊖⊖ **very low**[b]	One study reported on diabetic ketoacidosis, with 0/452 participants in the group who had their drug dosage reduced versus 0/226 participants in the usual care group experiencing a diabetic ketoacidosis event.

All-cause mortality	**Not reported**	—
Treatment satisfaction	**Not reported**	—
HbA1c (%) Follow-up: end of Ramadan	**Not reported**	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **HbA1c**: glycosylated haemoglobin A1c; **T1DM**: type 1 diabetes mellitus.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[*]Assumed risk was derived from the event rates in the comparator groups.
[a]Downgraded by two levels because of risk of bias (performance bias, detection bias), and by one level because of imprecision (small number of studies).
[b]Downgraded by one level because of risk of bias (detection bias), and by two levels because of serious imprecision (no events reported).

BACKGROUND

The Muslim faith has approximately 1.5 billion followers and is one of the fastest-growing faiths in the world (Hackett 2015). Annually, Muslims of pubertal age and older are obligated to observe the Ramadan fast. This involves abstaining from the consumption of food and fluids from dawn to dusk daily for about 30 days (Rashed 1992). The duration of daily fasting depends on the local daylight hours where the individual is residing. This can be up to 22 hours, depending on the geographical location and the climatic season in which the month of Ramadan falls. Muslims who are travelling, menstruating, pregnant or breastfeeding are exempt from fasting during Ramadan (Sakr 1975). Exemptions also exist for people who are ill, including those with chronic medical conditions such as diabetes.

Description of the condition

Type 2 diabetes is a global health concern with a considerable impact on human life and health expenditure. Recent global estimates suggest that nearly 462 million people are living with type 2 diabetes, which represents a prevalence of approximately 6.3% (Khan 2020). Estimates in several large Muslim-majority countries suggest that the prevalence of type 2 diabetes in these countries is even higher and is expected to increase further in the next decade (IDF 2021; Khan 2020).

Many people with type 2 diabetes choose to fast during the Ramadan period. The lack of food and fluids during fasting increases the risk of dehydration and hypoglycaemia among people with type 2 diabetes. In addition, an individual's food habits tend to change during Ramadan in relation to the proportion of fat, protein and carbohydrates eaten (Shatila 2021). There is also a general tendency to ingest food with high carbohydrate and sugar content during Ramadan, and this heightens the risk of developing hyperglycaemia among people with diabetes (Salti 2004). As such, many interventions have been developed to ensure the optimal care of people with type 2 diabetes during Ramadan. These include Ramadan-focused education and medication adjustment (Ibrahim 2015). However, Ramadan fasting by people with type 2 diabetes still represents a challenge for healthcare professionals as management guidelines are expert-based (Hassanein 2022; IDF 2016).

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study conducted in 2001 found that nearly four out of five people with type 2 diabetes mellitus (T2DM) fasted for at least 15 days during Ramadan (Salti 2004). Fasting during Ramadan heralds a sudden shift in meal times, meal quantity, meal quality, sleep pattern and physical activity. Meal times are mainly nocturnal, and this affects sleep quality and quantity. In people with type 2 diabetes, abstaining from food and fluid during fasting also leads to dehydration and increases the risk of hypoglycaemia. Indeed, in the EPIDIAR study, the risk of hypoglycaemia increased by 7.5 times in these individuals (Salti 2004). However, due to the long fasting hours, there is a tendency to consume meals high in carbohydrates during fast-breaking (Iftār). In addition, as the general atmosphere of the Ramadan month is a celebration, fasting during the day is often followed by a feast with a variety of food in the evening, including those with high sugar content. This increases the risk of hyperglycaemia and diabetic ketoacidosis among people with diabetes (Salti 2004). As such, most trials on Ramadan fasting in people with type 2 diabetes have primarily focused on strategies that are intended to ensure that these individuals remain euglycaemic during this period, as well as those that reduce the risk of developing hypoglycaemia.

Description of the intervention

Over the past few years, several guidelines and diabetes management programmes have been developed to improve diabetes care, especially among those who wish to fast during Ramadan (Hassanein 2016; Hassanein 2022; Ibrahim 2015). This can be achieved through interventions such as Ramadan-focused education or changing or adjusting pharmacological agents that have a higher risk of hypoglycaemia for another class of pharmacological agents with a lower risk of hypoglycaemia (IDF DAR 2021)

Ramadan-focused education

A cornerstone of managing diabetes during Ramadan is patient education, which increases patients' understanding of their condition to prevent or delay complications, which can improve quality of life. Ramadan-focused education is an extension of this and provides additional knowledge on the necessary adjustments needed for the month of Ramadan. The objective of Ramadan-focused education is to raise awareness of people with diabetes to understand the risk associated with diabetes and fasting and recognise any symptoms of mild or severe complications when fasting. In particular, educational content should include, as a minimum, information on the importance of effective management of diabetes during Ramadan, such as the timing of blood glucose monitoring, advice on nutritional intake, medication adjustment, and advice on physical activities and exercise during Ramadan.

The current recommendation is that people with diabetes who wish to fast during Ramadan should consult their healthcare professional between six and eight weeks before the start of Ramadan. In the assessment, healthcare professionals will then determine the appropriateness of fasting and provide advice, taking into consideration their cultural preferences. During this visit, it is important that individuals are educated on the importance of self-glucose monitoring to empower them to better identify and prevent episodes of hypoglycaemia. Individuals should also be educated on the misconception that blood-glucose monitoring invalidates fasting (Lee 2017b).

As the fasting and feasting nature of Ramadan encourages the consumption of large carbohydrate meals and sugary drinks, this can impact blood glucose levels, which potentially increases the risk of complications in people with diabetes. Therefore, dietary advice should include meal planning and steps to follow a healthy balanced diet. Advice to avoid rigorous exercise, especially during the few hours before breaking fast (before sunset), should also be provided since it may lead to an increased risk of hypoglycaemia and dehydration (Hassanein 2022). This information is important to achieve safe fasting during Ramadan as it helps people with diabetes recognise symptoms of mild and severe complications when fasting, thus allowing them to break their fast if necessary.

Several trials have examined the use of diabetes-focused education targeted at those who wish to fast during Ramadan. Recent studies have demonstrated that Ramadan-focused diabetes education was beneficial in reducing the risk of hypoglycaemia in those who

fast as it improves confidence in diabetes management as well as psychosocial factors when fasting (Bravis 2010; Lee 2017b).

Adjustment of pharmacological hypoglycaemic agents

The class of medication an individual is taking for the management of diabetes can influence the risk of developing hypoglycaemia during Ramadan. In particular, people with type 2 diabetes who are on insulin or an insulin secretagogue, such as sulfonylureas, are at higher risk of developing hypoglycaemia due to an altered diet during Ramadan. As such, several trials have focused on the role of switching pharmacotherapy or reducing the dose of insulins to reduce the risk of hypoglycaemia (Kieu 2022; Lee 2016). For example, studies have examined the use of dipeptidyl-peptidase-4 (DPP-4) inhibitors such as vildagliptin or sitagliptin as well as glucagon-like peptide 1 (GLP-1) analogues such as exenatide or liraglutide for people with type 2 diabetes who fast during Ramadan due to their lower risk of developing hypoglycaemia (Lee 2016; Loh 2016). Other studies have also examined the use of short-acting insulin secretagogues such as repaglinide. Due to the short duration of action, these agents have been used during Ramadan since they carry a low risk of hypoglycaemia (Anwar 2006).

Adverse effects of the intervention

While most interventions have focused on reducing the risk of hypoglycaemia in individuals who fast during Ramadan, at the same time there is an increased risk of developing hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis (Hassanein 2016; Ibrahim 2015).

In addition to potential adverse effects from fasting, adverse effects may also be related to the type of pharmacological hypoglycaemic agent. The most common adverse effect associated with the use of sulfonylurea and insulins is hypoglycaemia. Both therapies are also associated with weight gain, while insulin use is associated with injection site reactions (Palmer 2016). DPP-4 inhibitors, meanwhile, are associated with gastrointestinal disturbances. With regard to GLP-1 analogues, nausea is common but wears off with time. No serious adverse effects have yet been proven, but there has been concern about exenatide and liraglutide causing pancreatitis (Cao 2020; Palmer 2016). Due to the short nature of the intervention, the long-term adverse effects will not be reviewed.

How the intervention might work

Diabetes-focused education has been shown to improve individuals' knowledge and understanding of diabetes as well as their self-efficacy skills. In addition, a review has suggested that organisational quality improvement strategies, such as case management or even team changes, can improve glycaemic control in people with type 2 diabetes (Tricco 2012). This has been shown to improve a wide variety of outcomes, including improved diet control, increased physical activities and drug adherence (Allah 2018; Lee 2017b). In addition, trials have shown that oral hypoglycaemic agents, especially sulphonylureas, increase the risk of hypoglycaemia among people with type 2 diabetes (Zammitt 2005). This risk is especially heightened during Ramadan, due to the need to fast for prolonged periods. As such, trials have further examined the role of switching people with type 2 diabetes to non-sulphonylurea-based pharmacotherapies such as DPP-4 inhibitors to reduce the risk of hypoglycaemia amongst these individuals (Lee 2016).

Why it is important to do this review

Over the past few years, the number of Muslim individuals who choose to fast during Ramadan has increased and is predicted to increase further in the coming decade (Pew Research 2017). As such, it is important that an effective guideline for the management of people with type 2 diabetes who fast during Ramadan is available. The recent International Diabetes Federation (IDF) and Diabetes and Ramadan (DaR) International Alliance (IDF-DAR) Practical Guidelines provide a practical tool to help healthcare professionals safely guide people with diabetes who wish to fast during Ramadan. The guidelines cover several topics, including epidemiology, the physiology of fasting, risk stratification, nutrition advice, medication adjustment and the implementation of recommendations (Hassanein 2022). However, most of the existing recommendations have largely been based on expert opinion rather than evidence from existing clinical studies.

While several recently published systematic reviews have examined strategies to optimise health outcomes during Ramadan (Lee 2016; Tourkmani 2021), these reviews have not comprehensively examined all potentially important patient outcomes, such as all-cause mortality. Other recent reviews have also included a mixture of studies, including randomised controlled trials (RCTs) and observational studies, which limits the strength of evidence generated (Gad 2020; Gad 2021; Gad 2022). In addition, since the publication of these reviews, several new trials have been published (Azar 2016; Wan Seman 2016). As such, there is a need to comprehensively synthesise these data from RCTs to help guide the work of healthcare professionals. In this review, we will only focus on people with type 2 diabetes since there is a scarcity of detailed consensus guidance or clinical trials for people with type 1 diabetes who wish to fast in Ramadan.

OBJECTIVES

To assess the effects of interventions for people with type 2 diabetes fasting during Ramadan.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs).

Types of participants

All people with type 2 diabetes mellitus (T2DM) who fast during Ramadan.

Types of interventions

We investigated the interventions aimed at improving the care of people with T2DM who fast during Ramadan, including organisational, pharmacological or educational interventions.

Usual care was defined as standard care that individuals with T2DM should receive according to national guidelines.

We investigated the following comparisons of intervention versus control/comparator.

Intervention

- Any organisational intervention/strategy implemented during Ramadan (such as changes to the structure or organisation of the primary healthcare team including adding a team member or using a multidisciplinary team).
- Any changes to glucose-lowering medications during Ramadan (such as switching from sulphonylurea to a dipeptidyl-peptidase-4 inhibitor (DPP4-I)).
- Any educational intervention (such as Ramadan-focused diabetes education) implemented before or during Ramadan.

Comparator

- Usual care or no intervention compared with any of the above-mentioned interventions.

Concomitant interventions must be the same in both the intervention and comparator groups to establish fair comparisons. If a trial included multiple arms, we included any trial arm that met the inclusion criteria.

Minimum duration of intervention

For interventions that involved change of glucose-lowering medications, the intervention would need to be at least 30 days duration or longer (i.e. started before Ramadan and continued until the end of Ramadan). For educational interventions and organisational interventions, we did not place a restriction on the duration of intervention.

Minimum duration of follow-up

The minimal duration of follow-up required was at least 30 days (Ramadan fasting period). We defined any follow-up period that continued beyond the original timeframe for the primary outcome measure, as specified in the power calculation of the trial's protocol, as an extended follow-up period (also called an open-label extension study) (Buch 2011; Megan 2012).

Types of outcome measures

We included a trial even if it failed to report one or more of our primary or secondary outcome measures; however, if it reported none of our primary or secondary outcomes, we excluded the trial but provided some basic information in an additional table.

We investigated the following outcomes using the methods and time points specified below.

Primary outcomes

- Hypoglycaemic episodes.
- Health-related quality of life.
- Adverse events other than hypoglycaemia.

Secondary outcomes

- All-cause mortality.
- Glycosylated haemoglobin A1c (HbA1c).
- Blood pressure.
- Lipids.
- Body weight.
- Treatment satisfaction.
- Self-care behaviours.

Method of outcome measurement

- Hypoglycaemic episodes: classified as mild (self-managed), moderate (daily activities interrupted but self-managed) or severe (requiring assistance from others).
- Health-related quality of life: evaluated by a validated instrument, such as the diabetes-specific quality of life scale (DSQoLs) questionnaire.
- Adverse events other than hypoglycaemic episodes: such as anxiety and depression.
- All-cause mortality: death from any cause.
- HbA1c: measured in % or mmol/mol.
- Blood pressure: systolic and diastolic blood pressure measured in mmHg.
- Lipids: serum cholesterol (total cholesterol, high-density lipoprotein (HDL-) cholesterol and low-density lipoprotein (LDL-) cholesterol).
- Body weight: measured in kilograms (kg).
- Treatment satisfaction: evaluated by a validated instrument, such as the diabetes treatment satisfaction questionnaire (DTSQ).
- Self-care behaviours: evaluated with a validated instrument, such as summary of diabetes self-care activities (SDSCA).

Timing of outcome measurement

- For hypoglycaemic episodes, adverse events other than hypoglycaemic episodes and all-cause mortality: any time after participants were randomised to the intervention/comparator groups.
- For health-related quality of life, HbA1c, blood pressure, lipids, body weight, treatment satisfaction and self-care behaviours: short-term (up to three months after Ramadan fasting) and midterm (longer than three months after Ramadan fasting).

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to 29 June 2022 and placed no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO).
- Ovid MEDLINE(R) ALL (1946 to 28 June 2022).
- PsycINFO Ovid (1806 to June week 3 2022).
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch/).

We did not include Embase in our search, as RCTs indexed in Embase were prospectively added to CENTRAL via a highly sensitive screening process (Cochrane 2022). The detailed search strategies can be found in Appendix 1.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included

trials, systematic reviews, meta-analyses and health technology assessment reports. In addition, we contacted the authors of included trials to identify any additional information on the retrieved trials and establish whether we may have missed further trials.

We did not use abstracts or conference proceedings for data extraction. This is because this information source did not fulfil the CONSORT requirements, which consist of "an evidence-based, minimum set of recommendations for reporting randomised trials" (CONSORT 2018; Scherer 2007). We presented information on abstracts or conference proceedings in the Characteristics of studies awaiting classification table.

Data collection and analysis

Selection of studies

Two review authors (SWHL and RS) independently screened the abstract or title, or both, of every record retrieved from the literature searches, to determine the trials that were to be further assessed. We obtained the full text of all potentially relevant records. We resolved any disagreements through consensus or by recourse to a third review author (NML). In the event that we could not resolve a disagreement, we categorised the trial as a 'study awaiting classification' and contacted the trial authors for clarification. We presented an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009). We listed all articles excluded after full-text assessment in the Characteristics of excluded studies table and provided the reasons for exclusion.

Data extraction and management

For trials that fulfilled our inclusion criteria, two review authors (SWHL and RS or NML) independently extracted key participant and intervention characteristics. We described the interventions using the 'template for intervention description and replication' (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017).

We reported the data on efficacy outcomes and adverse events using standardised data extraction sheets from Cochrane Metabolic & Endocrine Disorders. We resolved any disagreements by discussion or, if required, consulted a third review author (NML) (for details see Characteristics of included studies; Table 1; Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15).

We provided information about potentially relevant ongoing trials, including trial identifier, in the Characteristics of ongoing studies table and in Appendix 8 'Matrix of trial endpoint (publications and trial documents)'. We tried to find the protocol for each included trial, and we reported in Appendix 8 the primary, secondary and other outcomes in comparison with the data in the publications.

We emailed all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We presented the results of this survey in Appendix 16 and sought any relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximised the information yielded by collating all available data. We used the most complete data set of aggregated data across all known publications. We listed the duplicate publications, companion documents, multiple reports of a primary trial and trial documents for included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we also listed duplicate publications, companion documents, multiple reports of a trial and trial documents for excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials were available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trial register but no additional information (study results, publication, or both) was available, we added this trial to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Two review authors (NML and RS) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus or by consulting a third review author (SWHL). In the case of disagreement, we consulted the rest of the review author team and made a judgement based on consensus. If adequate information was unavailable from the publications, trial protocols or other sources, we contacted the trial authors to request more detail on missing risk of bias items.

We used the Cochrane risk of bias assessment tool (Higgins 2017), and assigned assessments of low, high or unclear risk of bias. We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein (Higgins 2017).

Summary assessment of risk of bias

We presented a risk of bias graph and a risk of bias summary figure.

We distinguished between self-reported and investigator-assessed and adjudicated outcome measures.

We considered the following self-reported outcomes.

- Hypoglycaemic episodes.
- Health-related quality of life.
- Adverse events other than hypoglycaemic episodes.
- Treatment satisfaction (including satisfaction with the intervention).
- Self-care behaviours.
- Blood pressure.
- Body weight.

We considered the following outcomes to be investigator-assessed.

- Hypoglycaemic episodes.
- Adverse events other than hypoglycaemic episodes.
- All-cause mortality.

- HbA1c.
- Blood pressure.
- Lipids.
- Body weight.

Risk of bias for a trial across outcomes

Some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we marked all endpoints investigated in the associated trial as being at high risk.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains, and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

We defined outcomes as being at low risk of bias when most information came from trials at low risk of bias, unclear risk when most information came from trials at low or unclear risk of bias, and high risk when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two included trials were available for a comparison of a given outcome, we expressed the dichotomous data as a risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg) we estimated the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we calculated the standardised mean difference (SMD).

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison or reduced the sample size so that the same participants did not contribute multiple times (splitting the 'shared' group into two or more groups). Although the latter approach offers some solution for adjusting the precision of the comparison, it does not account for correlation arising from inclusion of the same set of participants in multiple comparisons (Higgins 2011).

We attempted to re-analyse cluster-RCTs that had not been appropriately adjusted for potential clustering of participants within clusters in their analyses. Variance of the intervention effects is inflated by a design effect. Calculation of a design effect involved estimation of an intra-cluster correlation (ICC). We obtained estimates of ICCs by contacting the trial authors, or by imputing ICC values using either estimates from other included trials that report ICCs or external estimates from empirical research (e.g. Bell 2013). We examined the impact of clustering by performing sensitivity analyses.

Dealing with missing data

If possible, we obtained missing data from the authors of included trials. We carefully evaluated important numerical data such as screened, randomly assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

For trials in which the standard deviation (SD) of the outcome was not available at follow-up, or we could not re-create it, we standardised by the mean of the pooled baseline SD from trials that reported this information.

When included trials did not report means and SDs for outcomes, and we did not receive requested information from trial authors, we imputed these values by estimating the mean and the variance from the median, the range and the size of the sample (Hozo 2005).

We investigated the impact of imputation on meta-analyses by performing sensitivity analyses, and reported every outcome for which trials had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we found heterogeneity, we attempted to determine possible reasons for this by examining individual trial and subgroup characteristics.

Assessment of reporting biases

As none of the analyses included 10 or more trials for a particular outcome, we did not assess small-trial effects (Sterne 2011; Sterne 2017).

Data synthesis

We undertook a meta-analysis when we judged participants, interventions, comparisons and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence showed homogeneous effects across trials, we summarised the low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects (Borenstein 2017a; Borenstein 2017b; Higgins 2009). We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and we undertook the following subgroup analyses including investigation of interactions (Altman 2003).

- Gender: as we expected that men and women may respond differently to the management.
- Age: the risk of hypoglycaemia is higher among those who are older. As such, we used 60 years as a cutpoint.
- Trial location: as Ramadan falls during the summer period, individuals fasting in countries located in the Northern Hemisphere will fast for up to 19 hours. This is expected to increase the risk of hypoglycaemia in these countries as opposed to trials conducted in the tropics or Southern Hemisphere.
- Treatment group: in individuals who use insulin, the risk of hypoglycaemia and weight gain can be higher compared to those who are on oral glucose-lowering agents.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published trials.
- Effect of risk of bias, as specified in the Assessment of risk of bias in included studies section.
- Very long or large trials, to establish the extent to which they dominate the results.
- Use of the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other) or country.

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and also to external validity, such as directness of results. Two review authors (NM, RS) independently rated the certainty of the evidence for each outcome. We resolved differences in assessment by discussion or by consultation with a third review author (SWHL). We presented results for outcomes as described in the Types of outcome measures section. When meta-analysis was not possible, we presented the results in a narrative format in the summary of findings table. We justified all decisions to downgrade the certainty of the evidence by using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review when necessary.

We presented a summary of the evidence in a summary of findings table (Meader 2014). This provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the summary of findings table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), along with the Review Manager (RevMan 5.3 and RevMan web) table editor (GRADEproGDT 2015; RevMan 2014).

Interventions presented in the summary of findings table included any organisational intervention/strategy implemented during Ramadan, any changes to glucose-lowering medications during Ramadan, and any educational intervention implemented before or during Ramadan. Comparators were usual care or no intervention.

We reported the following outcomes, listed according to priority.

- Hypoglycaemic episodes
- Health-related quality of life
- Adverse events other than hypoglycaemic episodes
- All-cause mortality
- Treatment satisfaction (including satisfaction with the intervention)
- HbA1c

RESULTS

Description of studies

For a detailed description of studies, see the Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification sections.

Results of the search

Our search strategy identified 665 records, and three additional references were identified through other sources (cross-checking the reference lists of included trials). After deduplication, 531 records remained (see Figure 1). A total of 47 potentially eligible articles were identified after screening of title and abstracts. Of these, we excluded 17 after full-text review. We included 30 records describing 17 RCTs that met our inclusion criteria. Three ongoing studies will need to be incorporated in a future update of this review (Aghili 2012; Mohamad 2018; Yusoff 2017).

Figure 1.

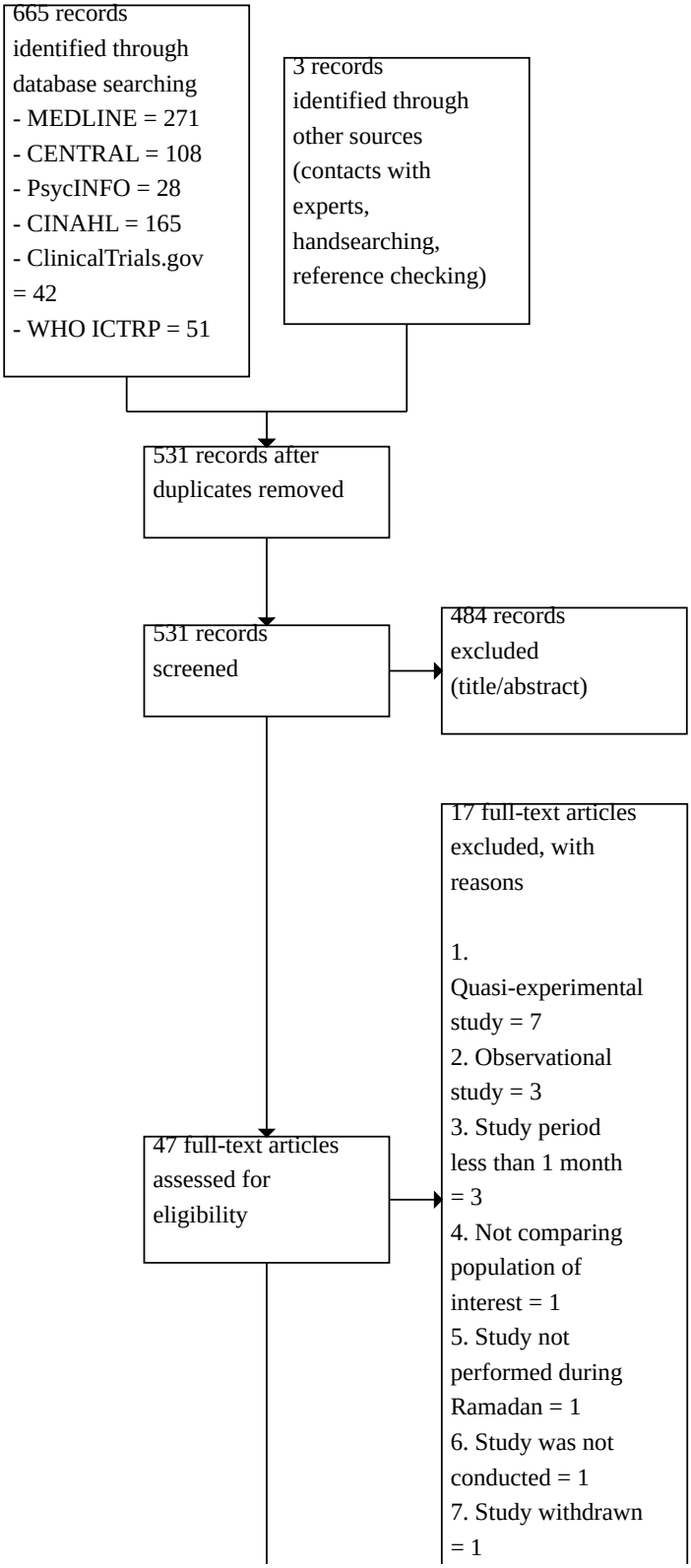
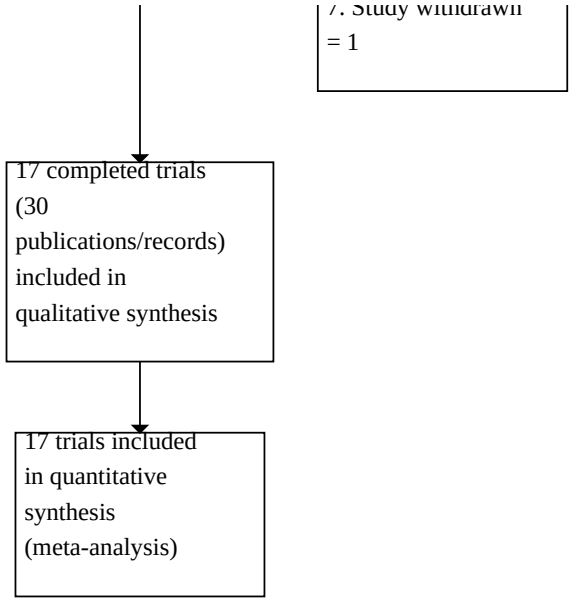


Figure 1. (Continued)



Included studies

A detailed description of the studies is presented elsewhere (see Table 1; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15; Appendix 17). A summary is presented below.

Source of data

All trials included in the current review were published in medical journals. We contacted all authors or investigators of included trials by email (see Appendix 16). Seven authors responded to our request and provided additional data and clarifications.

Comparisons

The 17 studies that provided relevant data for this review covered eight comparisons as follows:

- Four trials compared dipeptidyl-peptidase 4 (DPP-4) inhibitors with sulphonylureas (Al-Sifri 2011; Aravind 2012; Hassanein 2014; Mahla 2014).
- Two trials compared the use of meglitinides with sulphonylureas (Anwar 2006; Mafauzy 2002).
- One trial compared sodium-glucose co-transporter-2 (SGLT-2) inhibitors with sulphonylureas (Wan Seman 2016).
- Three trials compared glucagon-like peptide-1 (GLP-1) analogues with sulphonylureas (Azar 2016; Brady 2014; Hassanein 2019).
- Two trials compared insulin analogues with biphasic insulin (Hassanein 2018; Shehadeh 2015).
- Two trials compared telemedicine with usual care (Lee 2015; Lee 2017a).
- Two trials compared Ramadan-focused patient education with usual care (Belkhadir 1993; Lum 2018).
- One trial compared dosage reduction of four commonly used multidrug regimens compared to usual care (Zaghlol 2021).

Trial design

Of the 17 trials, 15 were parallel RCTs (Al-Sifri 2011; Anwar 2006; Aravind 2012; Azar 2016; Belkhadir 1993; Brady 2014; Hassanein 2014; Hassanein 2018; Hassanein 2019; Lee 2015; Lum 2018; Mafauzy 2002; Mahla 2014; Wan Seman 2016; Zaghlol 2021), and two were cluster-randomised parallel RCTs (Lee 2017a; Shehadeh 2015). All trials reported a run-in period of between four and 12 weeks, with a duration of intervention of four weeks during the Ramadan period and a follow-up of at least four weeks. The trials were performed between the years 1993 and 2019. Seven trials were multi-centre trials performed in at least two or more countries (Al-Sifri 2011; Aravind 2012; Azar 2016; Hassanein 2014; Hassanein 2018; Hassanein 2019; Mafauzy 2002). The remaining trials were performed in Malaysia (n = 4; Anwar 2006; Lee 2015; Lee 2017a; Wan Seman 2016), Singapore (n = 1; Lum 2018), Morocco (n = 1; Belkhadir 1993), United Kingdom (n = 1; Brady 2014), Israel (n = 1; Shehadeh 2015), and Jordan (n = 1; Zaghlol 2021). One trial did not specify the study location (Mahla 2014). Twelve trials reported that they had received commercial funding (Al-Sifri 2011; Aravind 2012; Azar 2016; Belkhadir 1993; Brady 2014; Hassanein 2014; Hassanein 2018; Hassanein 2019; Mafauzy 2002; Mahla 2014; Shehadeh 2015; Wan Seman 2016). Three trials received non-commercial funding (Lee 2015; Lee 2017a; Lum 2018), while two trials did not report the funding source (Anwar 2006; Zaghlol 2021). None of the trials was terminated before the planned end of follow-up.

Settings

Three trials were performed in a primary care clinic setting (Lee 2015; Lee 2017a; Shehadeh 2015). One trial were performed in an outpatient setting (Al-Sifri 2011), while another two trials were performed in clinics and hospital settings (Belkhadir 1993; Hassanein 2019). One trial was performed in an endocrine clinic

setting (Anwar 2006), one was performed in a tertiary hospital setting (Zaghlol 2021), and two trials were performed in primary care and hospital setting (Lum 2018; Wan Seman 2016). The setting was not described in seven studies (Aravind 2012; Azar 2016; Brady 2014; Mafauzy 2002; Hassanein 2014; Hassanein 2018; Mahla 2014) (see Appendix 5).

Participants

Overall, 5359 participants with type 2 diabetes participated in the 17 included trials (See Table 1). Sample sizes ranged from 37 (Lee 2015) to 1066 (Al-Sifri 2011). Where reported, 76% to 97% of randomised participants completed the trials to the end. Only one trial did not report the dropout rates (Lum 2018).

Two trials included only people from Asia; one included only Malaysians (Lee 2015), while another included mainly Indians, Bangladeshis and Pakistanis (Brady 2014). Two trials included participants from different ethnicities, including Asians, Blacks or Africans and Whites (Azar 2016; Hassanein 2018). Thirteen trials did not report information about ethnicity (Al-Sifri 2011; Anwar 2006; Aravind 2012; Belkhadir 1993; Hassanein 2014; Hassanein 2019; Lee 2017a; Lum 2018; Mafauzy 2002; Mahla 2014; Shehadeh 2015; Wan Seman 2016; Zaghlol 2021) (see Appendix 5). Two studies did not report the gender of the participants in each intervention group (Mahla 2014; Lum 2018). For the remaining 15 trials that provided information on gender, both men and women were included (Al-Sifri 2011; Anwar 2006; Aravind 2012; Azar 2016; Belkhadir 1993; Brady 2014; Hassanein 2014; Hassanein 2018; Hassanein 2019; Lee 2015; Lee 2017a; Mafauzy 2002; Shehadeh 2015; Wan Seman 2016; Zaghlol 2021). One trial did not report the age of the participants (Lum 2018). The age of the included participants varied from 30 to 74 years (see Appendix 6). For studies that reported baseline HbA1c levels of participants, baseline HbA1c varied from 6.9% to 13.7%. All, but one trial reported body mass index (BMI) at baseline (Lum 2018). BMI varied from 26.5 kg/m^2 to 33.1 kg/m^2.

Inclusion/exclusion criteria

All 17 trials recruited participants with type 2 diabetes, aged 18 years and above, who expressed interest in fasting for at least 15 days during the Ramadan period. However, two trials did not report exclusion criteria (Anwar 2006; Mahla 2014). For the remaining trials, major exclusion criteria were women being pregnant or lactating and having a diagnosis of renal, hepatic, mental and cardiac diseases (see Appendix 3).

Interventions

Ten trials evaluated newer anti-hyperglycaemic agents with the aim to assess their suitability as the main agent to be used during Ramadan. These included DPP-4 inhibitors (Al-Sifri 2011; Aravind 2012; Hassanein 2014; Mahla 2014), GLP-1 analogues (Azar 2016; Brady 2014; Hassanein 2019), meglitinides (Anwar 2006; Mafauzy 2002), or SGLT-2 inhibitors (Wan Seman 2016). Of these, two trials used sitagliptin 100 mg taken daily compared to a sulphonylurea (Al-Sifri 2011; Aravind 2012); one trial used vildagliptin 50 mg compared to gliclazide (Hassanein 2014); and one trial used vildagliptin 50 mg taken twice-daily compared to long-acting sulphonylurea (glimepiride or gliclazide) (Mahla 2014). Two trials used repaglinide 4 mg three times daily with glibenclamide (Anwar 2006; Mafauzy 2002), while one trial used dapagliflozin 10 mg daily compared to a sulphonylurea (Wan Seman 2016). One trial used liraglutide 1.2 mg daily compared to a sulphonylurea (Brady 2014); one used liraglutide 1.8 mg daily compared to a sulphonylurea (Azar 2016); and one trial used lixisenatide 20 µg daily with basal insulin and metformin compared to sulphonylurea with basal insulin and metformin (Hassanein 2019).

Other studies evaluated different insulin regimens to assess their suitability in Ramadan, in view of the challenges in following regular insulin regimens with the changes in diet. One trial examined the use of another analogue with biphasic insulin (Hassanein 2018); and another study used insulin detemir with biphasic insulin compared to standard care (Shehadeh 2015).

Additionally, two trials aimed to optimise their participants' medication regimen through Ramadan-focused education together with empowerment (Belkhadir 1993; Lum 2018). Two trials used telemedicine to remotely monitor and provide advice to their patients in an attempt to influence the participants' attitudes and behaviour (Lee 2015; Lee 2017a). One trial evaluated the impact of dosage adjustment of four different commonly used drug regimens during Ramadan (Zaghlol 2021). For full details of the intervention, see Appendix 4.

Outcomes

All 17 trials had specified either rates of hypoglycaemia or the proportion of participants with hypoglycaemia as one of the primary or secondary outcomes in their study (Appendix 7). Eight trials reported on severe hypoglycaemia events (Al-Sifri 2011; Aravind 2012; Azar 2016; Brady 2014; Hassanein 2014; Hassanein 2018; Hassanein 2019; Wan Seman 2016; see Appendix 15). Two trials also reported nocturnal hypoglycaemia events (Azar 2016; Hassanein 2018; see Appendix 15). All but three trials (Belkhadir 1993; Brady 2014; Mafauzy 2002) provided a definition for a hypoglycaemic event, which varied between studies (see Appendix 11). These included experiencing any clinical symptoms such as faintness, dizziness, headache, confusion, anxiety, sweating, tremor, palpitation or nausea which is suggestive of hypoglycaemia. Several trials also included the presence of asymptomatic hypoglycaemia as part of their definition for a hypoglycaemic event, which is the presence of blood glucose levels below a pre-defined threshold. The threshold varied from 3.9 mmol/L to 3.1 mmol/L. Six trials also included a definition for severe/serious hypoglycaemia (Al-Sifri 2011; Azar 2016; Brady 2014; Hassanein 2018; Lee 2017a; Lum 2018), while two trials included a definition for nocturnal hypoglycaemia (Azar 2016; Hassanein 2018) (see Appendix 12; Appendix 13; Appendix 14; Appendix 15).

Adverse events other than hypoglycaemia was reported in 11 studies (Al-Sifri 2011; Aravind 2012; Azar 2016; Brady 2014; Hassanein 2014; Hassanein 2018; Hassanein 2019; Mafauzy 2002; Shehadeh 2015; Wan Seman 2016; Zaghlol 2021; see Appendix 12; Appendix 14). Similarly, serious adverse events were reported in nine studies (Al-Sifri 2011; Aravind 2012; Azar 2016; Hassanein 2014; Hassanein 2018; Hassanein 2019; Mafauzy 2002; Shehadeh 2015; Wan Seman 2016). Another five trials reported on discontinuation rates due to adverse events (Aravind 2012; Azar 2016; Hassanein 2014; Hassanein 2019; Mafauzy 2002). Two trials also reported on discontinuation rates due to at least one hospitalisation event (Azar 2016; Wan Seman 2016).

Ten trials reported on the changes in glycosylated haemoglobin after the intervention (Belkhadir 1993; Brady 2014; Hassanein 2014; Hassanein 2019; Lee 2017a; Lum 2018; Mafauzy 2002; Mahla 2014;

Shehadeh 2015; Wan Seman 2016). Five trials also reported the change in fasting plasma glucose (Lee 2015; Lee 2017a; Lum 2018; Mahla 2014; Wan Seman 2016), while another five trials reported the change in serum fructosamine (Azar 2016; Lee 2017a; Mafauzy 2002; Shehadeh 2015; Wan Seman 2016).

Information on other outcomes, such as all-cause mortality, blood pressure, lipids, body weight, treatment satisfaction or self-care behaviours, was insufficient or lacking in most of the included trials. Two trials included the patient-reported quality of life (Lee 2017a; Shehadeh 2015; see Appendix 17). Death was reported in four trials (Al-Sifri 2011; Aravind 2012; Hassanein 2014; Hassanein 2018). Only one study reported on blood pressure (Lee 2017a), while another four trials reported the changes in blood lipids (Brady 2014; Lee 2015; Lee 2017a; Shehadeh 2015). Five trials reported changes in body weight (Belkhadir 1993; Brady 2014; Hassanein 2014; Hassanein 2019; Lee 2017a), while two trials reported the change in body mass index (Lee 2017a; Mahla 2014). One study reported on self-care behaviour (Lee 2017a), and another study reported on treatment satisfaction (Brady 2014).

Excluded studies

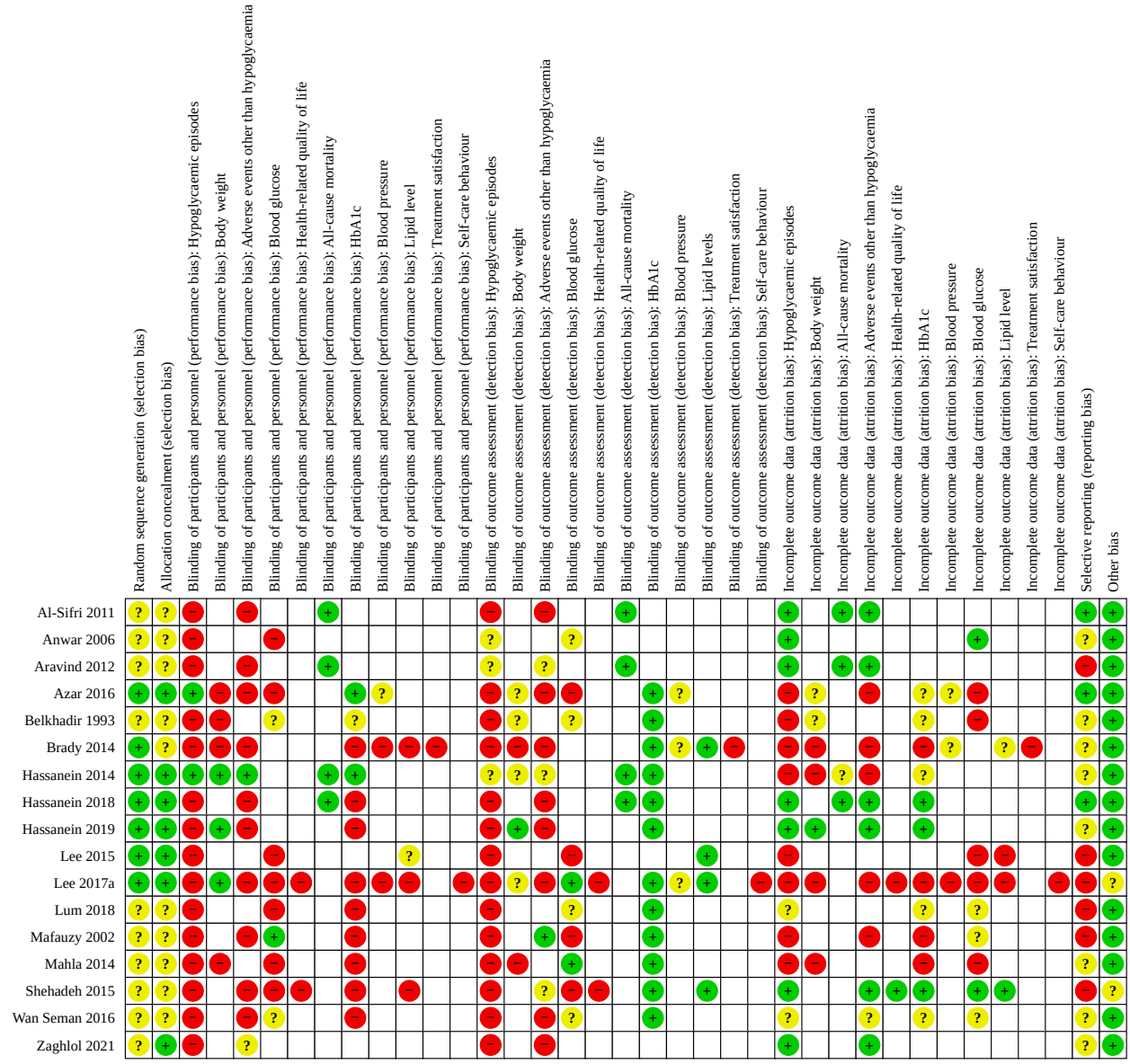
We excluded 17 articles or records after full-text evaluation (Figure 1). These references are listed in Characteristics of excluded studies. A total of seven trials were excluded as these were quasi-randomised studies (Hajjaji 2019; Japar 2022; Khamseh 2013; Mohamed 2019; Prataksitorn 2014; Susilparat 2014; Shafras 2020). Three trials were excluded as they were observational studies (Cesur 2007; Glimiperide Study Group 2005; McEwen 2015). Two trials were excluded as these had been withdrawn (Institut de Recherches International Servier 2007; NCT02694263), while another two articles were excluded as the study duration was less than 30 days (Akram 1999; Mattoo 2003). One study was excluded due to the wrong population (IRCT201702269856N5), while another trial was excluded as it was not conducted during the Ramadan period (NCT00664534).

Risk of bias in included studies

Overall, the risk of bias profile of the included studies poses a major concern, as all studies have at least one major domain each with high and unclear risks of bias. Blinding of outcome assessment in the outcome of hypoglycaemic episodes represents the subdomain with the worst overall risk of bias profile with 15 studies having high and only two having low risks of bias respectively. The blinding of outcome assessment for both all-cause mortality and HbA1c represents the subdomain with the best risk of bias profile. The overall risk of bias profile of the review, displayed according to the domain and study, is shown in the risk of bias graph (Figure 2) and summary (Figure 3), respectively, and the support for judgement of the risk of bias assessment of each included study is available in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (blank cells indicate that the particular outcome was not measured in some studies).

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (blank cells indicate that the particular outcome was not measured in some studies).



Allocation

All included studies were RCTs. Regarding the method of random sequence generation, 10 studies had unclear and seven had low risk of bias. For allocation concealment, 10 studies had unclear and seven had low risk of bias. Studies with low risk of bias in random sequence generation and allocation concealment either used a voice-response interactive system, computer-generated random numbers or other form of randomisation scheme that was generated by a person independent of allocation. Six out of 17 studies had low risk of selection bias by virtue of having low risk of bias in both random sequence generation and allocation concealment (Azar 2016; Hassanein 2014; Hassanein 2018; Hassanein 2019; Lee 2015; Lee 2017a). The remaining studies had an overall unclear risk of selection bias as the information provided was insufficient to assess the risk of bias in one or both domains under this category.

Blinding

For the primary outcomes of hypoglycaemia episodes and adverse effects, we considered all but one study (Hassanein 2014) to have high risk of bias for blinding of participants and personnel, and for the other two major outcomes of body weight and blood glucose, the vast majority of the included studies had high risk of bias. We considered the studies as having high risk of performance bias

because they were either stated to be open-label or non-blinded, or because of the obviously different interventions received by each study group with no documented attempt to mask the participants from the intervention they received. We judged Hassanein 2014 to have low risk of performance bias because the authors stated that participants "received either vildagliptin or gliclazide in a double-blind, double-dummy fashion".

In terms of blinding of outcome assessors for the outcomes evaluated, the vast majority of the included studies had high risk and the remaining had unclear risk of bias, as in all studies the main assessors were the participants themselves, who were not blinded to the allocated intervention. Only one study had low risk of bias for blood glucose, as this was reported to have been measured objectively in a laboratory (Lee 2017a). Furthermore, in all trials that conducted assessment of HbA1c, this was conducted in laboratories and thus blinded outcome assessment was assumed, and we therefore considered these studies to carry a low risk of detection bias. We also considered all-cause mortality to carry a low risk of performance and detection bias, since the possibility of subjective interference is minimal for this outcome measure.

Incomplete outcome data

Overall, seven studies had low, eight high and two unclear risk of bias in the domain of incomplete primary outcome data. The risk of bias of each study is largely consistent across the outcomes assessed in this domain. The main concerns were the absolute high dropout rates or dropout rates deemed sufficiently high to substantially affect the direction and/or magnitude of the effect using the worst case scenario approach.

Selective reporting

Three studies had low risk, six high risk and the remaining eight unclear risk of bias in this domain. In studies rated as low risk, all pre-specified or expected outcomes were reported in sufficient detail. In studies rated as high risk, there was inconsistency between the reporting of pre-specified outcomes in the protocol and the published paper. Studies with unclear risk had no protocol available to cross-check consistency of outcomes between the protocol and published paper.

Other potential sources of bias

We judged two studies to have unclear risk and the remaining 15 to have low risk of other biases. In this category, we rated studies as having unclear risk as there were certain unclear risk domains specific to cluster-RCT due to recruitment of participants and how the clusters were allocated (Lee 2017a; Shehadeh 2015). While there was involvement of the pharmaceutical industry in two studies (Al-Sifri 2011; Aravind 2012), we did not identify any potential interference, write-up or monitoring of the trial. As such, we rated these studies as having low risk of other bias.

Effects of interventions

See: **Summary of findings 1** DPP-4 inhibitors versus sulphonylureas; **Summary of findings 2** Meglitinides versus sulphonylureas; **Summary of findings 3** SGLT-2 inhibitors versus sulphonylureas; **Summary of findings 4** GLP-1 analogues inhibitors versus sulphonylureas; **Summary of findings 5** Insulin analogues versus biphasic insulin; **Summary of findings 6** Telemedicine versus usual care; **Summary of findings 7** Patient education versus usual care; **Summary of findings 8** Drug dosage reduction versus usual care

The baseline characteristics of trial participants are listed in Appendix 5 and Appendix 6.

DPP-4 inhibitors versus sulphonylureas

Primary outcome

Hypoglycaemic episodes

Four trials reported data on hypoglycaemic episodes (Al-Sifri 2011; Aravind 2012; Hassanein 2014; Mahla 2014). DPP-4 inhibitors may lower the risk of non-serious hypoglycaemia among participants compared to sulphonylureas (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.41 to 0.68; 2495 participants; $I^2 = 0\%$; Analysis 1.1; low-certainty evidence).

Three studies reported serious hypoglycaemia, with two studies reporting no events (Al-Sifri 2011; Aravind 2012). A total of 6/127 participants in the DPP-4 inhibitors group and 4/1219 in the sulphonylureas group experienced a serious hypoglycaemic event. With the two studies that reported zero serious hypoglycaemic events excluded from the pooled analysis, the evidence suggests that DPP-4 inhibitors may result in little to no difference in the risk of experiencing a serious hypoglycaemic event compared to sulphonylureas, but the evidence is very uncertain (RR 1.49, 95% CI 0.43 to 5.24; 557 participants; Analysis 1.2; very low-certainty evidence).

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

Three studies reported adverse events other than hypoglycaemic episodes (Al-Sifri 2011; Aravind 2012; Hassanein 2014). The use of DPP-4 inhibitors may have little to no effect on the risk of experiencing any adverse events other than hypoglycaemic episodes compared to sulphonylureas but, again, the evidence is very uncertain (RR 0.90, 95% CI 0.52 to 1.54; 2426 participants; $I^2 = 72\%$, Analysis 1.3; very low-certainty evidence).

Secondary outcomes

All-cause mortality

Three studies reported on all-cause mortality (Al-Sifri 2011; Aravind 2012; Hassanein 2014) (2426 participants; Analysis 1.4; moderate-certainty evidence). In all three studies, none of the participants in the DPP-4 inhibitor group died, and none of the participants in the sulphonylurea group died.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

Two studies reported change in HbA1c (Hassanein 2014; Mahla 2014). The use of DPP-4 inhibitors may have little to no effect on the change in HbA1c compared to sulphonylureas, but the evidence is very uncertain (mean difference (MD) -0.11%, 95% CI -0.57% to 0.36%; 626 participants; Analysis 1.5; $I^2 = 76\%$; very low-certainty evidence).

Anthropometric measures: body weight

One study reported body weight (Hassanein 2014). In the DPP-4 inhibitor group, participants lost on average 1.9 kg (standard deviation (SD) 0.2) compared to 1.7 kg (SD 0.2) in the sulphonylurea group (Analysis 1.6).

Anthropometric measures: body mass index

One study reported on body mass index (BMI) (Mahla 2014). In the DPP-4 inhibitor group, the mean post-intervention BMI was 28.83 kg/m^2 (SD 4.72) compared with 29.79 kg/m^2 (SD 3.87) in the sulphonylurea group (Analysis 1.7).

Glycaemic control: fasting plasma glucose

One study reported the change in fasting plasma glucose (Mahla 2014). In the DPP-4 inhibitor group, the mean fasting plasma glucose was 7.4 mmol/L (SD 3.0) compared to 7.8 mmol/L (SD 2.6) in the sulphonylurea group (Analysis 1.8)

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

Meglitinides versus sulphonylurea

Primary outcome

Hypoglycaemic episodes

Two studies reported data on hypoglycaemic episodes (Anwar 2006; Mafauzy 2002). Although the evidence is very uncertain, meglitinides may make little to no difference to the risk of experiencing non-serious hypoglycaemia compared to sulphonylureas (RR 0.72, 95% CI 0.40 to 1.28; 273 participants; I^2 = 0%; Analysis 2.1; very low-certainty evidence).

None of the included trials reported on serious hypoglycaemia.

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

None of the included trials reported this outcome.

Secondary outcomes

All-cause mortality

None of the included trials reported this outcome.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

One study reported change in HbA1c (Mafauzy 2002). The use of meglitinides may increase HbA1c compared to sulphonylureas (MD 0.38%, 95% CI 0.35% to 0.41%; 235 participants; Analysis 2.2; very low-certainty evidence)

Glycaemic control: serum fructosamine

One study reported the change in serum fructosamine (Mafauzy 2002). In the DPP-4 inhibitor group, the mean serum fructosamine was reduced by 16.9 mmol/L (SD 4.9) compared to a reduction of 6.92 mmol/L (SD 4.8) in the sulphonylurea group (Analysis 2.3)

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

SGLT-2 inhibitors versus sulphonylurea

Primary outcome

Hypoglycaemic episodes

One trial reported data on hypoglycaemic episodes (Wan Seman 2016). SGLT-2 inhibitors use may lower the risk of non-serious hypoglycaemia among participants compared to sulphonylurea (RR 0.28, 95% CI 0.10 to 0.79; 110 participants; Analysis 3.1; low-certainty evidence).

One trial reported serious hypoglycaemia (Wan Seman 2016). SGLT-2 inhibitor use may have little to no effect on the risk of experiencing a serious hypoglycaemic event compared to sulphonylurea, but the evidence is very uncertain (RR 0.90, 95% CI 0.06 to 13.97; 110 participants; Analysis 3.2; very low-certainty evidence).

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

One trial reported data on adverse events (Wan Seman 2016). The evidence is very uncertain about an effect of SGLT-2 inhibitors on the risk of experiencing any adverse events other than hypoglycaemic episodes compared to sulphonylurea use (RR 1.00, 95% CI 0.60 to 1.67; 110 participants; Analysis 3.3; very low-certainty evidence)

Secondary outcomes

All-cause mortality

None of the trials reported on this outcome.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

One trial reported data on HbA1c (Wan Seman 2016). The use of a SGLT-2 inhibitor may have little to no effect on HbA1c compared to sulphonylurea (MD 0.27%, 95% CI -0.04% to 0.58%; 110 participants; Analysis 3.4; low-certainty evidence)

Anthropometric measures: body weight

None of the trials reported on this outcome.

Anthropometric measures: body mass index

None of the trials reported on this outcome.

Glycaemic control: serum fructosamine

One study reported the change in serum fructosamine (Wan Seman 2016). In the SGLT-2 inhibitor group, the mean serum fructosamine was reduced by 2.98 mmol/L (SD 55.14) compared to a reduction of 39.35 mmol/L (SD 51.98) in the sulphonylurea group (Analysis 3.5)

Glycaemic control: fasting plasma glucose

One trial reported data on fasting plasma glucose (Wan Seman 2016). In the SGLT-2 inhibitor group, the mean fasting plasma glucose was increased by 0.20 mmol/L (SD 2.53) compared to a reduction of 0.43 mmol/L (SD 2.50) in the sulphonylurea group (Analysis 3.6).

Subgroup and sensitivity analyses

As only one study for this comparison was found, neither subgroup nor sensitivity analyses could be performed.

GLP-1 analogues versus sulphonylurea

Primary outcome

Hypoglycaemic episodes

Three trials reported data on hypoglycaemic episodes (Azar 2016; Brady 2014; Hassanein 2019). GLP-1 analogue use may lower the risk of non-serious hypoglycaemia among participants compared to sulphonylurea (RR 0.45, 95% CI 0.28 to 0.74; 596 participants; I^2 = 0%; Analysis 4.1; low-certainty evidence).

Three studies reported serious hypoglycaemia, with two studies reporting no events (Azar 2016; Brady 2014). In total 0/291 participants in the GLP-1 analogue group and 1/305 in the sulphonylurea group experienced a severe hypoglycaemic event. As such, with the two trials that reported zero severe hypoglycaemic events excluded from the pooled analysis, GLP-1 analogue use may result in little to no difference in the risk of experiencing a serious hypoglycaemic event compared to sulphonylureas, but the evidence is very uncertain (RR 0.33, 95% CI 0.01 to 7.99; 181 participants; Analysis 4.2; very low-certainty evidence).

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

Two studies reported adverse events (Azar 2016; Hassanein 2019). Although the evidence is very uncertain, the use of GLP-1 analogues may have little to no effect on the risk of experiencing adverse events other than hypoglycaemic episodes compared to sulphonylureas (RR 1.50, 95% CI 0.86 to 2.61; 499 participants; I^2 = 71%; Analysis 4.3; very low-certainty evidence)

Secondary outcomes

All-cause mortality

None of the trials reported on this outcome.

Treatment satisfaction

One trial reported on treatment satisfaction, using a diabetes treatment satisfaction questionnaire (Brady 2014) (Appendix 18). The use of GLP-1 analogues may have little to no effect on treatment satisfaction compared to sulphonylurea, but the evidence is very uncertain (MD -0.18%, 95% CI -3.18% to 2.82%; 62 participants; Analysis 4.4; very low-certainty evidence).

Glycosylated haemoglobin A1c

Two trials reported data on HbA1c at the end of study (Brady 2014; Hassanein 2019). GLP-1 analogue use may have little to no effect on HbA1c compared to sulphonylurea use (MD 0.04%, 95% CI -0.45% to 0.36%; 246 participants; I^2 = 66%; Analysis 4.5; low-certainty evidence).

Lipids: total cholesterol

One study reported the change in total cholesterol levels (Brady 2014). In the GLP-1 analogue group, the mean total cholesterol was reduced by 0.003 mmol/L (SD 0.80) compared to a reduction of 0.13 mmol/L (SD 0.61) in the sulphonylurea group (Analysis 4.6).

Lipids: triglycerides

One study reported the change in triglyceride levels (Brady 2014). In the GLP-1 analogue group, the mean triglyceride level was decreased by 0.38 mmol/L (SD 1.53) compared to a decrease of 0.56 mmol/L (SD 1.28) in the sulphonylurea group (Analysis 4.7).

Anthropometric measures: body weight

Two trials reported data on body weight (Brady 2014; Hassanein 2019). GLP-1 analogue use may slightly lower body weight compared to sulphonylureas (MD -1.61 kg, 95% CI -3.67 to 0.44; 246 participants; I^2 = 86%; Analysis 4.8).

Anthropometric measures: body mass index

None of the trials reported on this outcome.

Glycaemic control: serum fructosamine

One study reported the change in serum fructosamine (Azar 2016). In the GLP-1 analogue group, the mean serum fructosamine was reduced by 12.80 mmol/L (SD 41.74) compared to a reduction of 16.40 mmol/L (SD 41.74) in the sulphonylurea group (Analysis 4.9).

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

Insulin analogues versus biphasic insulin

Primary outcome

Hypoglycaemic episodes

Two trials reported data on hypoglycaemic episodes (Hassanein 2018; Shehadeh 2015). Although the evidence is very uncertain, the use of insulin analogues may make little to no difference to the risk of experiencing non-serious hypoglycaemia compared to biphasic insulin (RR 0.43, 95% CI 0.13 to 1.40; 500 participants; I^2 = 85%, Analysis 5.1; very low-certainty evidence).

One study reported data on serious hypoglycaemia (Hassanein 2018). The use of insulin analogues may make little to no difference to the risk of experiencing a serious hypoglycaemic event compared to biphasic insulin but, again, the evidence is very

uncertain (RR 1.35, 95% CI 0.31 to 5.93; Analysis 5.2; very low-certainty evidence).

Health-related quality of life

One trial reported the change in quality of life score, using a visual analogue scale (Appendix 17), but no clear difference between treatment groups was observed (Shehadeh 2015).

Adverse events other than hypoglycaemic episodes

Two studies reported adverse events (Hassanein 2018; Shehadeh 2015). The use of insulin analogues may make little to no difference to the risk of experiencing any adverse events other than hypoglycaemic episodes compared to biphasic insulin (RR 0.83, 95% CI 0.44 to 1.56; 500 participants; I^2 = 83%, Analysis 5.3; very low-certainty evidence).

Secondary outcomes

All-cause mortality

One study reported on all-cause mortality (Hassanein 2018). One death was reported in the insulin analogue group and no deaths were reported in the biphasic insulin group (RR 3.02, 95% CI 0.12 to 73.53; 263 participants; Analysis 5.4; very low-certainty evidence).

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

One trial reported data on HbA1c at the end of study (Shehadeh 2015). The evidence is very uncertain about the effect of insulin analogues on HbA1c levels (MD 0.03%, 95% CI -0.17% to 0.23%; 245 participants; Analysis 5.5; very low-certainty evidence).

Lipids: total cholesterol

One study reported the change in total cholesterol levels at the end of study (Shehadeh 2015). In the insulin analogue group, the mean total cholesterol was increased by 0.05 mmol/L (SD 0.78) compared to a reduction of 0.07 mmol/L (SD 0.83) in the biphasic insulin group (Analysis 5.6).

Lipids: low-density lipoprotein

One study reported the change in low-density lipoprotein levels at the end of study (Shehadeh 2015). In the insulin analogue group, the mean low-density lipoprotein was decreased by 0.14 mmol/L (SD 0.72) compared to an equal decrease of 0.14 mmol/L (SD 0.67) in the biphasic insulin group (Analysis 5.7).

Lipids: high-density lipoprotein

One study reported the change in high-density lipoprotein levels at the end of study (Shehadeh 2015). In the insulin analogue group, the mean high-density lipoprotein was decreased by 0.04 mmol/L (SD 0.23) compared to a decrease of 0.06 mmol/L (SD 0.18) in the biphasic insulin group (Analysis 5.8).

Lipids: triglycerides

One study reported the change in triglyceride levels at the end of study (Shehadeh 2015). In the insulin analogue group, the mean triglyceride level was decreased by 0.20 mmol/L (SD 0.97) compared to an increase of 0.39 mmol/L (SD 1.07) in the biphasic insulin group (Analysis 5.9).

Anthropometric measures: body weight

None of the trials reported on this outcome.

Anthropometric measures: body mass index

None of the trials reported on this outcome.

Glycaemic control: serum fructosamine

One study reported the change in serum fructosamine at the end of study (Shehadeh 2015). In the insulin analogue group, the mean serum fructosamine was reduced by 0.17 mmol/L (SD 0.82) compared to a reduction of 0.20 mmol/L (SD 0.72) in the biphasic insulin group (Analysis 5.10).

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

Telemedicine versus usual care

Primary outcome

Hypoglycaemic episodes

Two trials reported data on hypoglycaemic episodes (Lee 2015; Lee 2017a). The use of telemedicine may reduce the risk of non-serious hypoglycaemia among participants compared to usual care, but the evidence is very uncertain (RR 0.42, 95% CI 0.24 to 0.74; 121 participants; I^2 = 0%, Analysis 6.1; very low-certainty evidence).

None of the included trials reported on serious hypoglycaemia.

Health-related quality of life

One study reported data on health-related quality of life, based on the EurQol-5D-3L instrument (Lee 2017a) (Appendix 17). The evidence is very uncertain about the effect of telemedicine on health-related quality of life compared to usual care (MD 0.06, 95% CI -0.03 to 0.15; Analysis 6.2; very low-certainty evidence).

Adverse events other than hypoglycaemic episodes

None of the included trials reported this outcome.

Secondary outcomes

All-cause mortality

None of the trials reported on this outcome.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

One trial reported data on HbA1c (Lee 2017a). The use of telemedicine may have little to no effect on HbA1c compared to usual care (MD -0.84%, 95% CI -1.51% to -0.17%; 85 participants; Analysis 6.3; very low-certainty evidence).

Blood pressure: systolic blood pressure

One study reported the change in systolic blood pressure (Lee 2017a). In the telemedicine group, the mean systolic blood pressure

was increased by 4.40 mmHg (SD 22.63) compared to a decrease of 0.97 mmHg (SD 24.73) in the usual care group (Analysis 6.4).

Blood pressure: diastolic blood pressure

One study reported the change in diastolic blood pressure (Lee 2017a). In the telemedicine group, the mean diastolic blood pressure was decreased by 6.20 mmHg (SD 15.78) compared to a decrease of 6.17 mmHg (SD 9.07) in the usual care group (Analysis 6.5).

Lipids: total cholesterol

Two studies reported the change in total cholesterol levels (Lee 2015; Lee 2017a). Telemedicine may have little to no effect on total cholesterol levels compared to usual care (MD -0.28 mmol/L, 95% CI -1.08 mmol/L to 0.53 mmol/L; 121 participants; I^2 = 91%, Analysis 6.6).

Lipids: low-density lipoprotein

Two studies reported the change in low-density lipoprotein levels (Lee 2015; Lee 2017a). Telemedicine may result in little to no effect on low-density lipoprotein levels compared to usual care (MD 0.01 mmol/L, 95% CI -0.09 mmol/L to 0.11 mmol/L; 121 participants; I^2 = 0%; Analysis 6.7).

Lipids: high-density lipoprotein

Two studies reported the change in high-density lipoprotein levels (Lee 2015; Lee 2017a). Telemedicine may result in little to no effect on high-density lipoprotein levels compared to usual care (MD 0.00 mmol/L, 95% CI -0.06 mmol/L to 0.06 mmol/L; 121 participants; I^2 = 0%; Analysis 6.8).

Lipids: triglycerides

Two studies reported the change in triglyceride levels (Lee 2015; Lee 2017a). Telemedicine may have little to no effect on triglyceride levels when compared to usual care (MD 0.05 mmol/L, 95% CI -0.28 mmol/L to 0.38 mmol/L; 121 participants; I^2 = 71%; Analysis 6.9).

Anthropometric measures: body weight

One trial reported data on post-intervention body weight (Lee 2017a). In the telemedicine group, the mean body weight was 72.21 kg (SD 13.13) compared to 77.66 kg (SD 13.4) in the usual care group (Analysis 6.10).

Anthropometric measures: body mass index

One trial reported data on body weight (Lee 2017a). In the telemedicine group, the mean body weight was 29.42 kg/m^2 (SD 5.92) compared to 30.49 kg/m^2 (SD 5.11) in the usual care group (Analysis 6.11).

Self-care behaviours: diabetes self-efficacy

One study reported data on diabetes self-efficacy, measured using the Diabetes Self-Efficacy Scale (Lee 2017a) (Appendix 18). In the telemedicine group, the diabetes self-efficacy score was reduced by 0.40 points (SD 3.82) compared to a reduction of 0.22 points (SD 3.86) in the usual care group (Analysis 6.12).

Self-care behaviours: diabetes-related distress

One study reported data on diabetes-related distress (Lee 2017a) (Appendix 18). In the telemedicine group, the diabetes-related distress score was reduced by 0.40 points (SD 0.84) compared to a reduction of 0.40 points (SD 0.95) in the usual care group (Analysis 6.13).

Glycaemic control: serum fructosamine

One study reported the change in serum fructosamine at the end of study (Lee 2015). In the telemedicine group, the mean serum fructosamine was reduced by 19.40 mmol/L (SD 9.80) compared to a decrease of 30.00 mmol/L (SD 6.40) in the usual care group (Analysis 6.14).

Glycaemic control: fasting plasma glucose

Two studies reported data on fasting plasma glucose at the end of study (Lee 2015; Lee 2017a). Telemedicine may have little to no effect on serum fasting plasma glucose when compared to usual care (MD -0.90 mmol/L, 95% CI -2.03 mmol/L to 0.23 mmol/L; 122 participants; I^2 = 59%; Analysis 6.15).

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

Patient education versus usual care

Primary outcome

Hypoglycaemic episodes

Two trials reported data on hypoglycaemic episodes (Belkhadir 1993; Lum 2018). Offering Ramadan-focused patient education may have little to no effect on the risk of non-serious hypoglycaemia compared to usual care, but the evidence is very uncertain (RR 1.17, 95% CI 0.82 to 1.66; 422 participants; I^2 = 0%, Analysis 7.1; very low-certainty evidence).

None of the included trials reported on serious hypoglycaemia.

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

None of the included trials reported this outcome.

Secondary outcomes

All-cause mortality

None of the trials reported on this outcome.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

Two trials reported data on HbA1c at the end of study (Belkhadir 1993; Lum 2018). Ramadan-focused patient education may have little to no effect on HbA1c compared to usual care, but the evidence is very uncertain (MD -0.40%, 95% CI -0.73% to -0.06%; 422 participants; I^2 = 23%, Analysis 7.2; very low-certainty evidence).

Glycaemic control: fasting plasma glucose

One study reported the change in fasting plasma glucose at the end of Ramadan (Lum 2018). In the Ramadan-focused patient education group, the mean serum fasting plasma glucose was decreased by 1.60 mmol/L (SD 2.50) compared to a decrease of 0.20 mmol/L (SD 2.10) in the usual care group (Analysis 7.3).

Anthropometric measures: body weight

One trial reported data on body weight (Belkhadir 1993). After the intervention, in the Ramadan-focused patient education group the mean body weight was 69.2 kg (SD 10.0) compared to 65.7 kg (SD 11.4) in the usual care group (Analysis 7.4).

Subgroup and sensitivity analyses

Due to the lack of data from trials, subgroup analyses by age, gender, comorbid condition and trial location could not be performed. Similarly, no sensitivity analyses were conducted, since the predefined study characteristics to base these analyses on did not vary, or varied insufficiently, between trials.

Drug dosage reduction versus usual care

Primary outcome

Hypoglycaemic episodes

One trial reported data on hypoglycaemic episodes (Zaghlol 2021). Dosage reduction of the drug regimen during Ramadan may reduce the risk of non-serious hypoglycaemia among participants compared to usual care, but the evidence is very uncertain (RR 0.18, 95% CI 0.11 to 0.30; 678 participants; Analysis 8.1; very low-certainty evidence).

None of the included trials reported on serious hypoglycaemia.

Health-related quality of life

None of the included trials reported this outcome.

Adverse events other than hypoglycaemic episodes

One trial reported data on the risk of developing diabetic ketoacidosis (Zaghlol 2021). With no events reported in either study arm, the evidence is very uncertain about an effect of drug dosage reduction versus usual care on the risk of adverse events other than hypoglycaemic episodes (Analysis 8.2; very low-certainty evidence).

Secondary outcomes

All-cause mortality

None of the trials reported on this outcome.

Treatment satisfaction

None of the trials reported on this outcome.

Glycosylated haemoglobin A1c

None of the trials reported on this outcome.

Glycaemic control: fasting plasma glucose

None of the trials reported on this outcome.

Subgroup and sensitivity analyses

As only one study for this comparison was found, neither subgroup nor sensitivity analyses could be performed.

DISCUSSION

Summary of main results

The aim of this review was to determine the effects of interventions for adults with type 2 diabetes who fast during Ramadan. Seventeen trials, which randomised a total of 5359 participants, met our inclusion criteria. Twelve included studies were of pharmacological interventions and compared the use of DPP-4 inhibitors (Al-Sifri 2011; Aravind 2012; Hassanein 2014; Mahla 2014), meglitinides (Anwar 2006; Mafauzy 2002), SGLT-2 inhibitors (Wan Seman 2016) and GLP-1 analogues (Azar 2016; Brady 2014; Hassanein 2019) with sulphonylurea or insulin analogue use with biphasic insulin (Hassanein 2018; Shehadeh 2015). Four studies were behavioural interventions, which compared telemedicine (Lee 2015; Lee 2017a) or Ramadan-focused patient education with usual care (Belkhadir 1993; Lum 2018). In one study, participants were managed by adjusting the dosage of four commonly used drug regimens for diabetes during Ramadan (Zaghlol 2021). All 17 included studies in this review reported the incidence of non-serious hypoglycaemia. Other primary outcomes, such as health-related quality of life and adverse events other than hypoglycaemia, were reported inconsistently by various studies. Similarly, the secondary outcomes of all-cause mortality, blood pressure, lipids, body weight, treatment satisfaction and self-care behaviours were reported inconsistently among studies included in this review. A summary of the main results according to the comparisons of interventions, following the framework and categories outlined in the summary of findings tables, is presented below.

DPP-4 inhibitors versus sulphonylureas

Four studies compared DPP-4 inhibitors with sulphonylureas, randomising a total of 2562 participants who wished to fast during Ramadan. Low-certainty evidence showed that the use of DPP-4 inhibitors probably reduced the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those on sulphonylureas. Three studies reported serious hypoglycaemia, two of which reported no events, while one study reported six participants in the DPP-4 inhibitor group versus four participants in the sulphonylurea group experiencing a serious hypoglycaemic event (very low-certainty evidence). There may be no difference between DPP-4 inhibitors and sulphonylureas concerning adverse event rates (three studies, very low-certainty evidence) and all-cause mortality rates (three studies, moderate-certainty evidence). Evidence for HbA1c was inconsistent and unclear. No data were available for quality of life and treatment satisfaction.

Meglitinides versus sulphonylureas

Two studies compared meglitinides with sulphonylureas, with a total of 276 participants who wished to fast during Ramadan randomised. Very low-certainty evidence showed that the use of meglitinides suggested little or no effect on the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those on sulphonylurea (two studies, very low-certainty evidence). There may be no difference between

meglitinides and sulphonylureas in reducing HbA1c levels but, again, the evidence was very uncertain (one study, very low-certainty evidence). No data were available for all-cause mortality, adverse event rates, quality of life and treatment satisfaction.

SGLT-2 inhibitors versus sulphonylureas

One study compared SGLT-2 inhibitors with sulphonylureas, with 119 participants who wished to fast during Ramadan randomised. Low-certainty evidence showed that the use of SGLT-2 inhibitors may reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those on sulphonylurea. There may be no difference between SGLT-2 inhibitors and sulphonylureas in reducing the risk of experiencing serious hypoglycaemia, adverse event rates and HbA1c (one study, very low-certainty evidence). No data were available for all-cause mortality, quality of life and treatment satisfaction.

GLP-1 analogues versus sulphonylureas

Three studies compared GLP-1 analogues with sulphonylureas, randomising a total of 626 participants who wished to fast during Ramadan. Low-certainty evidence showed that the use of GLP-1 analogues may reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those on sulphonylurea. Three studies reported serious hypoglycaemia, two of which reported no events while one reported one serious hypoglycaemia event in the sulphonylurea group only (low-certainty evidence). There may be little to no difference between GLP-1 analogues and sulphonylureas in reducing the risk of experiencing adverse event (three studies, very low-certainty evidence) and HbA1c (one study, very low-certainty evidence). No data were available for all-cause mortality, adverse event rates, quality of life and treatment satisfaction.

Insulin analogues versus biphasic insulin

Two studies compared insulin analogues with biphasic insulin, with 508 participants who wished to fast during Ramadan randomised. Very low-certainty evidence showed that the use of insulin analogue inhibitors may reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those on biphasic insulin, but the evidence is very uncertain. One study reported serious hypoglycaemia, with four participants in the insulin analogue group versus three participants in the biphasic insulin group experiencing a serious hypoglycaemic event (very low-certainty evidence). There may be no difference between insulin analogue inhibitors and biphasic insulin in reducing the risk of experiencing adverse events (two studies, very low-certainty evidence) and HbA1c (one study, very low-certainty evidence). No data were available for all-cause mortality, quality of life and treatment satisfaction.

Telemedicine versus usual care

Two studies compared telemedicine with usual care, with randomised 121 participants who wished to fast during Ramadan. Low-certainty evidence showed that the use of telemedicine may reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those in the usual care group. The evidence is very uncertain about any difference between telemedicine use and usual care in changing the quality of life (one study, very low-certainty evidence). The use of telemedicine may reduce HbA1c levels compared to usual care, but the evidence is very uncertain (very low-certainty evidence). No data were available for serious hypoglycaemic events, adverse events, all-cause mortality and treatment satisfaction.

Patient education versus usual care

Two studies compared Ramadan-focused patient education with usual care, with 427 participants who wished to fast during Ramadan randomised. Very low-certainty evidence showed that patient education may not reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those in the usual care group, but the evidence is very uncertain. Very low-certainty evidence showed that patient education may reduce HbA1c levels compared to usual care but, again, the evidence is very uncertain. No data were available for serious hypoglycaemic events, adverse events, all-cause mortality, quality of life and treatment satisfaction.

Drug dosage reduction versus usual care

One study compared a drug dosage reduction of glucose-lowering therapy with usual care, randomising 678 participants who wished to fast during Ramadan. Very low-certainty evidence showed that drug dosage reduction may reduce the risk of experiencing non-serious hypoglycaemia among those who fasted during Ramadan compared to those in the usual care group, but the evidence is very uncertain. No participants either group experienced diabetic ketoacidosis or other adverse events during the trial period (very low-certainty evidence). No data were available for serious hypoglycaemic events, change in HbA1c, all-cause mortality, quality of life and treatment satisfaction.

Overall completeness and applicability of evidence

This review summarises data from 17 published RCTs of different interventions to support people with type 2 diabetes who wish to fast during Ramadan and the effects on relevant health outcomes. There was no high-certainty evidence available for any of the outcomes in the comparisons we assessed to determine the potential benefits of different interventions.

The evidence in this review can be applied to people with type 2 diabetes in most countries as the included trials were conducted in a wide range of Islamic countries, although there was a relative lack of trials from lower-income countries such as those in the African continent.

We found that there was a lack of evidence for outcomes such as quality of life, blood pressure, lipids, treatment satisfaction and self-care behaviour. For example, only one study reported health-related quality of life as an outcome (Lee 2017a).

Although meeting the criteria set for inclusion in our review, the studies identified comparing the two behavioural interventions, telemedicine and Ramadan-focussed patient education, to usual care used different approaches and content. For example, the usual care component of the studies, which various healthcare practitioners delivered, was not reported in sufficient detail. Furthermore, since the sample sizes were very small, the study results should be interpreted with caution.

Finally, we could not investigate the impact of reporting bias due to the limited number of studies available for each comparison.

Quality of the evidence

We assessed the certainty of evidence using the GRADE methodology, and the results are presented in the summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8). Across all studies, the certainty of the evidence ranged from very low to low for the primary outcome of risk of experiencing hypoglycaemia. Similarly, for the other primary outcomes of health-related quality of life and adverse events, the certainty of the evidence was very low. For the secondary outcomes, the certainty of the evidence ranged from very low to moderate. We downgraded this evidence for imprecision, high risk of bias and inconsistency of results.

Risk of bias domains were frequently judged 'unclear' because the information required for grading was often not reported. Only 11 studies had been prospectively registered or published a protocol (Appendix 8). For some studies, we identified a risk of attrition bias, and not all studies were double-blinded. This was common for behavioural interventions. Due to the interactive nature of the intervention, it was very difficult to blind the intervention staff and participants to group allocation. However, to minimise detection bias, it should be possible to blind the outcome assessors.

Potential biases in the review process

We minimised potential bias throughout the review process firstly by ensuring that all relevant databases and published sources were searched for studies meeting our inclusion and exclusion criteria. Our search was not limited by language or year of publication, and we also continuously updated our search strategy to ensure all eligible studies were included. However, we cannot exclude the small possibility of missing unpublished RCTs. We had to exclude three studies from our analysis due to incomplete published information and/or no further information being provided by the authors. We did not identify any potential important sources of bias in the study selection, data extraction and analysis process.

Agreements and disagreements with other studies or reviews

To date, many other reviews have been published examining the use of different pharmacological and non-pharmacological treatments during Ramadan in people with type 2 diabetes. In the earliest review on this topic by Lee et al, the authors reported that the use of DPP-4 inhibitors could reduce the risk of hypoglycaemia (Lee 2016). This finding was similarly reported in subsequent reviews, which noted that participants taking DPP-4 inhibitors were less likely to develop symptomatic hypoglycaemia and severe hypoglycaemia compared to those taking sulfonylureas (Gad 2021; Loh 2016). Other similar published systematic reviews also examined different interventions, including the use of SGLT-2 inhibitors (Gad 2022), GLP-1 analogues (Gray 2015) or patient education (Gad 2020), but concur that there is insufficient evidence to support any intervention.

Nevertheless, there are several differences between our review and other reviews described previously. Unlike other reviews, which included studies irrespective of study design (Gad 2021; Loh 2016), we included only RCTs to get more reliable information, especially on patient-relevant outcome measures. Another difference from our review is the lack of identification by other studies of unpublished data, which provides substantial information in all our analyses.

Despite these differences, the reported results were similar. All authors reported a paucity of research in this area. They also found that few studies had performed power calculations, thus making the extrapolation of the results difficult (Almansour 2017; Gad 2020; Lee 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Among people with type 2 diabetes, there are many who wish to fast during Ramadan. However, they are at an increased risk of experiencing poor glycaemic control and hypoglycaemia. This review found that pharmacological and behavioural interventions may be effective in reducing the risk of developing hypoglycaemia, but the evidence is weak and lacking, especially in terms of quantity and quality. This affects our confidence in the certainty of evidence. It remains unclear at the moment which type of intervention best supports people with diabetes who wish to fast during Ramadan. Suitable interventions should enable Muslims with diabetes to continue to observe Ramadan without compromising their well-being.

Implications for research

This Cochrane Review identified several gaps in the evidence for this topic. First, despite the increasing burden of diabetes, there is not yet a strong evidence base to guide physicians on interventions that can appropriately be recommended to support people with type 2 diabetes who wish to fast. Second, current evidence on interventions is mostly limited to high- and middle-income countries and most low-income countries are not represented in this review due to the absence of primary studies. Third, the synthesis of evidence has been hampered by heterogeneity in the outcomes measured and reported. Given that the Muslim population is growing worldwide, well-conducted, sufficiently powered RCTs should be a priority for future research. Multi-centre studies could therefore be useful, as different cultures approach Ramadan differently, with several changes in routines and eating habits.

In addition to addressing the gaps above, future research is also needed on behaviour change interventions as these have been suggested as the most feasible intervention for low- and middle-income countries (LMIC) rather than pharmacological interventions. Indeed, there is also a need for future studies to establish the suitability and acceptability of these interventions in LMICs.

Our review was also not designed to compare the effectiveness of multiple treatments from different clinical trials. A network meta-analysis may be more feasible to make these comparisons when more high-quality studies are available to determine the most suitable intervention that could lead to lower hypoglycaemic rates and better glycaemic control during this period. Finally, most of the studies often do not examine the benefits of such interventions on other outcomes such as treatment satisfaction and quality of life, and these outcomes should be considered a priority for future research exploring the wider benefit of interventions to improve glycaemic control during Ramadan.

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- Sign-off Editor (final editorial decision): Brenda Bongaerts, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Sifri 2011

Study characteristics	
Methods	**Study design**: open-label, multi-centre randomised controlled trial
Participants	**Inclusion criteria**: Muslims with type 2 diabetes, who were treated with a stable dose of sulphonylurea (glimepiride, gliclazide (immediate or modified release) or glibenclamide (glyburide)) with or without metformin for at least the last 3 months prior to enrolment in the study, and had an HbA1c ≤ 10% at the screening visit. Patients had to express their intention to fast during Ramadan after receiving medical counselling regarding the risks of fasting **Exclusion criteria**: previously treated with antihyperglycaemic agents other than a sulphonylurea with or without metformin, had a history of severe hypoglycaemia or had contraindications to treatment with DPP-4 inhibitors **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged ≥ 18 years **Gender distribution**: 48.7: 51.3 (females:males ratio) **Countries where trial was performed**: 6 countries (Egypt, Israel, Jordan, Lebanon, Saudi Arabia and the United Arab Emirates)
Interventions	**Intervention**: sitagliptin 100 mg daily with or without metformin **Comparators**: pre-study sulphonylurea (glimepiride, gliclazide (immediate or modified release) or glibenclamide (glyburide)) with or without metformin **Duration of intervention**: 4 weeks **Duration of follow-up**: 2 weeks **Run-in period**: at least 5 weeks

Al-Sifri 2011 *(Continued)*

	Number of trial centres: 43
Outcomes	**Reported outcome(s) in full text of publication**: incidence of symptomatic hypoglycaemia, incidence of symptomatic and asymptomatic hypoglycaemia
Study details	**Trial identifier**: — **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Merck Sharp & Dohme) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "To compare the incidence of symptomatic hypoglycaemia in fasting Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "In this open-label study, eligible patients were randomised in a 1:1 ratio to either switch to sitagliptin 100 mg qd or to remain on their pre-study sulphonylurea (with or without metformin). For allocation to treatment group, each site was provided with a randomisation schedule." **Comment:** authors mention that participants were randomised in a 1:1 ratio, without detailing the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on the sequence generation methods and allocation to enable an assessment of the independence between the two
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Following randomisation, patients and investigators were not blinded to treatment, and the study proceeded under real-life conditions without any additional protocol-mandated intervention." **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** it was unclear who reported the adverse event - if this was reported by investigator or participants themselves; likely by participants as this was an open-label study and participants were not blinded to treatment allocation
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment:** this was an open-label study. However, the knowledge of the intervention assignment does not influence concomitant care and outcomes.
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Quote:** "For Ramadan, patients were provided with daily diary cards to record hypoglycaemic symptoms and complications, need for assistance due to symptoms of hypoglycaemia, time from consuming their last meal and time from taking their last medication dose to the start of the symptoms of hypoglycaemia and whether the fast was broken between dawn and dusk."

Al-Sifri 2011 *(Continued)*

		Comment: hypoglycaemic episodes were recorded by participants themselves who were not blinded to their treatment sequence allocation
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "All adverse events were rated by the study site investigators for intensity (mild, moderate or severe) and relationship to study drug. Patients were also contacted by phone 2 weeks after Ramadan to assess the occurrence of any serious adverse events since study end." **Comment:** adverse events were recorded by site investigators who were not blinded to treatment sequence allocation
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: the outcome was objectively measured and reported
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote:** "1021 out of 1066 patients (95.8%) randomised were analysed, with balanced number of missing data between the two groups." **Comment:** the reasons for dropouts (post-randomisation violation of eligibility criteria, incomplete diary card, withdrawal of consent) appeared acceptable
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** the reasons for dropouts (post-randomisation violation of eligibility criteria, incomplete diary card, withdrawal of consent) appeared acceptable
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "1021 out of 1066 patients (95.8%) randomised were analysed, with balanced number of missing data between the two groups." **Comment:** the reasons for dropouts (post-randomisation violation of eligibility criteria, incomplete diary card, withdrawal of consent) appeared acceptable
Selective reporting (reporting bias)	Low risk	**Comment:** major outcomes of symptomatic hypoglycaemia and low glucose readings were reported in sufficient detail as per study record
Other bias	Low risk	**Comment:** none identified

Anwar 2006

Study characteristics	
Methods	**Study design**: open-label, parallel randomised controlled trial
Participants	**Inclusion criteria**: Muslims who fulfilled the WHO criteria for type 2 diabetes mellitus, taking sulfonylurea either alone or in combination with metformin **Exclusion criteria**: — **Diagnostic criteria**: WHO criteria for type 2 diabetes **Setting**: endocrine clinics **Age group**: — **Gender distribution**: 58:42 (females:males ratio) **Country where trial was performed**: Malaysia
Interventions	**Intervention**: repaglinide titrated over 3 months to a dose of 4 mg 3 times daily

Anwar 2006 *(Continued)*

	Comparator: glimepiride titrated over 3 months to a dose of 6 mg daily **Duration of intervention**: 4 weeks **Duration of follow-up**: 1 month **Run-in period**: 3 months **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: incidence of hypoglycaemia, blood glucose levels
Study details	**Trial identifier**: — **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: none reported **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "The purpose of this study was to compare glycaemic control in Muslim type 2 diabetic patients treated with a post prandial agent (repaglinide) or a long acting SU (glimepiride) during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients were randomized block (4x4) into either repaglinide or glimepiride." **Comment:** authors mentioned that the participants were randomised in blocks (4 x 4) but no further details were provided on the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information on the sequence generation method and allocation to enable an assessment of the independence between the two
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Hypoglycaemic episodes were recorded as those with a blood glucose measurement of <3.1 mmol/L, in accordance with the definition of the American Diabetic Association." **Comment:** hypoglycaemic episodes were self-reported by participants who knew their treatment allocation
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Quote:** "The performance of each home blood glucose kit was checked and data in patients' diaries were transferred to record forms during each subsequent clinic visit." **Comment:** blood glucose measures were self-reported by participants who knew their treatment allocation
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	Unclear risk	**Comment:** it was unclear whether the assessors were blinded to the participant allocation status
Blinding of outcome assessment (detection bias)	Unclear risk	**Comment:** it was unclear whether the assessors were blinded to the participant allocation status

Anwar 2006 *(Continued)*
Blood glucose

Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote:** "38 out of 41 patients (92.7%) randomised were analysed. One patients could not fast due to illness, and two patients violated the protocol." **Comment:** although protocol violation did not constitute a valid reason for exclusion, the number was small
Incomplete outcome data (attrition bias) Blood glucose	Low risk	**Quote:** "38 out of 41 patients (92.7%) randomised were analysed. One patients could not fast due to illness, and two patients violated the protocol." **Comment:** although protocol violation did not constitute a valid reason for exclusion, the number was small
Selective reporting (reporting bias)	Unclear risk	**Comment:** no study protocol was available
Other bias	Low risk	**Comment:** none identified

Aravind 2012

Study characteristics	
Methods	**Study design**: multi-centre, parallel randomised controlled trial
Participants	**Inclusion criteria**: Muslims with type 2 diabetes who were at least 18 years of age, were treated with a stable dose of sulphonylurea (glimepiride, gliclazide (immediate- or modified-release), or glibenclamide) with or without metformin for at least 3 months, had an HbA1c 10% at the screening visit, with an intention to fast during Ramadan after receiving medical counselling regarding the risks of fasting and provided written informed consent **Exclusion criteria**: type 1 diabetes or gestational diabetes, were pregnant or breastfeeding, were treated with antihyperglycaemic agents other than a sulphonylurea with or without metformin, had a history of severe hypoglycaemia, had hypersensitivity or contraindications to treatment with DPP-4 inhibitors, had serum creatinine 1.5 mg/dL (males) or 1.4 mg/dL (females), would have difficulty completing study forms, or were currently participating in another intervention study **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 years and above **Gender distribution**: 53:47 (females:males ratio) **Countries where trial was performed**: 2 countries (Malaysia and India)
Interventions	**Intervention**: sitagliptin 100 mg daily with or without metformin **Comparators**: sulfonylurea (glimepiride, gliclazide (immediate- or modified-release), or glibenclamide) with or without metformin **Duration of intervention**: — **Duration of follow-up**: — **Run-in period**: — **Number of trial centres**: 25

Aravind 2012 *(Continued)*

Outcomes	**Reported outcome(s) in full text of publication**: symptomatic hypoglycaemic event, asymptomatic hypoglycaemic event, serious adverse event
Study details	**Trial identifier**: NCT01340768 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Merck Sharp & Dohme Corp) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "the present study assessed the incidence of hypoglycaemia during Ramadan in sulphonylurea-treated patients from India and Malaysia who were randomly switched to sitagliptin or remained on their pre-study sulphonylurea regimen."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "eligible patients were randomised in a 1:1 ratio to switch to sitagliptin 100 mg once daily (with or without metformin) or to remain on their current sulphonylurea treatment (with or without metformin)." **Comment:** the authors mentioned that participants were randomised in a 1:1 ratio, without detailing the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Quote:** "For allocation to treatment group, each site was provided with a randomisation schedule. Randomization was stratified by treatment regimen (monotherapy or in combination with metformin)" **Comment:** no information on the sequence generation methods and allocation to enable an assessment of the independence between the two
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Patients were provided with daily diary cards to record hypoglycaemic symptoms and complications, time from consuming their last meal and time from their last medication dose to the start of the symptoms of hypoglycaemia or need for assistance, and whether the fast was observed during the day" **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "Patients were also contacted by phone two weeks after Ramadan to assess the occurrence of any serious adverse events since study end." **Comment:** this was an open-label trial with self-reported outcomes including adverse events
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment:** open-label design with outcome measure unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	**Comment:** hypoglycaemic episodes were recorded by participants themselves, who were not blinded to their treatment sequence allocation

Aravind 2012 *(Continued)*

Hypoglycaemic episodes		
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** adverse events were self-reported by participants, who were not blinded to treatment sequence allocation
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment:** the outcome was objectively measured and reported.
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote:** "Of the randomised patients, 97% completed the study, with slightly more patients discontinuing sitagliptin during the study." **Comment:** 848 out of 870 participants (97%) completed the study. Reasons for missing data included loss to follow-up and consent withdrawal, which was considered appropriate
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** 848 out of 870 participants (97%) completed the study. Reasons for missing data included loss to follow-up and consent withdrawal, which was considered appropriate
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "Of the randomised patients, 97% completed the study, with slightly more patients discontinuing sitagliptin during the study." **Comment:** 848 out of 870 participants (97%) completed the study. Reasons for missing data included loss to follow-up and consent withdrawal, which was considered appropriate
Selective reporting (reporting bias)	High risk	**Comment:** prespecified secondary outcome was not reported in the publication
Other bias	Low risk	**Comment:** none identified

Azar 2016

Study characteristics	
Methods	**Study design**: multi-centre, parallel randomised controlled trial
Participants	**Inclusion criteria**: adults aged 18 to 80 years diagnosed with type 2 diabetes on stable diabetes treatment (metformin ≥ 1000 mg/d and sulphonylurea (gliclazide, glipizide or glyburide/glibenclamide) at maximum tolerated dose (at least half maximal approved dose) or glimepiride (≥ 2 mg/d)) ≥ 90 days prior to screening, who had glycated haemoglobin (HbA1c) 7% to 10% (53 to 86 mmol/mol), body mass index (BMI) ≥ 20 kg/m^2 and expressed intention to fast (dawn to sunset) during Ramadan 2014 after receiving counselling regarding the risk of fasting, and who were willing to give blood during Ramadan **Exclusion criteria**: previous treatment with glucose-lowering agent other than those stated in the inclusion criteria < 90 days prior to screening (insulin was not allowed except in connection with intercurrent illness and for ≤ 7 days) and any contraindication for successful and sustained fasting from a medical perspective at the investigator's discretion. Other criteria include known or suspected hypersensitivity to trial products or related products; previous participation in this trial defined as informed consent; female who is pregnant, breastfeeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods; participation in another clinical trial within 90 days prior to screening; any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardise the participant's safety or compliance with the protocol; history of chronic pancreatitis or idiopathic acute pancreatitis; screening calcitonin value ≥ 50 ng/L; personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; impaired liver function

Azar 2016 *(Continued)*

	(alanine amino transferase ≥ 2.5 times upper normal limit (UNL)); impaired renal function (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 per modification of diet in renal disease formula); any episode of unstable angina, acute coronary event, cerebral stroke/transient ischaemic attack or other significant cardiovascular event as judged by the investigator within 90 days prior to screening; heart failure (New York Heart Association (NYHA) class IV); uncontrolled hypertension (defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg); diagnosis of malignant neoplasm in the previous 5 years (except basal or squamous cell skin cancer); surgery scheduled for the trial duration period, excluding minor surgical procedures; use of any drug (except for those stated in the inclusion criteria), which at the discretion of the investigator, could interfere with the blood glucose level; known or suspected abuse of alcohol or drugs; mental inability, unwillingness or language barrier precluding adequate understanding of or compliance with study procedures; and any contraindication to liraglutide. **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 to 80 years **Gender distribution**: 50.7:49.3 (females:males ratio) **Countries where trial was performed**: 7 countries (Algeria, Israel, India, Lebanon, Malaysia, South Africa and United Arab Emirates)
Interventions	**Intervention**: liraglutide up to 1.8 mg/d + metformin **Comparators**: sulfonylurea (gliclazide, glipizide or glyburide/glibenclamide or glimepiride) + metformin **Duration of intervention**: 33 weeks **Duration of follow-up**: 1 week **Run-in period**: 2 week **Number of trial centres**: 39
Outcomes	**Reported outcome(s) in full text of publication**: symptomatic hypoglycaemic event, adverse event, serum HbA1c, weight, blood pressure, fasting plasma glucose, serum fructosamine
Study details	**Trial identifier**: NCT01917656 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "Compare effects of liraglutide 1.8 mg and sulphonylurea, both combined with metformin, on glycaemic control in patients with type 2 diabetes (T2D) fasting during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Eligible patients were randomised using an interactive web/voice response system (IV/IWRS) in a 1:1 manner to either switch from their pre-trial sulphonylurea to liraglutide, with dose escalation from 0.6 to 1.8 mg/d, or con-

Azar 2016 *(Continued)*

		tinue with their pre-trial sulphonylurea at the already established MTD, both combined with metformin."
Allocation concealment (selection bias)	Low risk	**Quote:** "Eligible patients were randomised using an interactive web/voice response system (IV/IWRS) in a 1:1 manner to either switch from their pre-trial sulphonylurea to liraglutide, with dose escalation from 0.6 to 1.8 mg/d, or continue with their pre-trial sulphonylurea at the already established MTD, both combined with metformin." **Comment:** sequence was concealed using an interactive voice system, which was managed centrally
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	Low risk	**Quote:** "Subjects were to record in the patient diary fasting self-measured plasma glucose (SMPG), using the plasma glucose (PG) meter provided, on a weekly basis or more frequently at the investigator's discretion. If any fasting SMPG measurement met the limits of unacceptable hyperglycaemia (see File S1, withdrawal criteria), the subject was to contact the investigator" **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Body weight	High risk	**Comment:** this was an open-label trial, but there was no information on how body weight was measured
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "Treatment-emergent adverse events (TEAEs) and hypoglycaemic episodes were assessed at all phone contacts and site visits." **Comment:** this was an open-label trial with self-reported outcome of adverse events
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Quote:** "Subjects were to record in the patient diary fasting self-measured plasma glucose (SMPG), using the plasma glucose (PG) meter provided, on a weekly basis or more frequently at the investigator's discretion. If any fasting SMPG measurement met the limits of unacceptable hyperglycaemia (see File S1, withdrawal criteria), the subject was to contact the investigator." **Comment:** this was an open-label trial with self-reported outcome where participants reported the measured plasma glucose levels
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Comment:** this was an open-label study. The knowledge of the intervention assignment might have influenced concomitant care and outcomes.
Blinding of participants and personnel (performance bias) Blood pressure	Unclear risk	**Comment:** this was an open-label study. The knowledge of the intervention assignment might have influenced concomitant care and outcomes.
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Quote:** "Subjects were to record in the patient diary fasting self-measured plasma glucose (SMPG), using the plasma glucose (PG) meter provided, on a weekly basis or more frequently at the investigator's discretion. If any fasting SMPG measurement met the limits of unacceptable hyperglycaemia (see File S1, withdrawal criteria), the subject was to contact the investigator." **Comment:** hypoglycaemic episodes were recorded by participants themselves, who were not blinded to their treatment sequence allocation

Azar 2016 *(Continued)*

Blinding of outcome assessment (detection bias) Body weight	Unclear risk	**Comment:** body weight was measured at the end of treatment during clinic visits by the investigators
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "Treatment-emergent adverse events (TEAEs) and hypoglycaemic episodes were assessed at all phone contacts and site visits." **Comment:** adverse events were self-reported by participants themselves, who were not blinded to their treatment sequence allocation
Blinding of outcome assessment (detection bias) Blood glucose	High risk	**Quote:** "Subjects were to record in the patient diary fasting self-measured plasma glucose (SMPG), using the plasma glucose (PG) meter provided, on a weekly basis or more frequently at the investigator's discretion" **Comment:** the outcome was self-reported based upon self-reporting by participants
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory
Blinding of outcome assessment (detection bias) Blood pressure	Unclear risk	**Comment:** blood pressure was measured at the end of treatment during clinic visits by the investigators
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "The statistical evaluation followed the intention-to-treat principle, and subjects contributed to the evaluation "as randomised". " **Comment:** 50 participants withdrew from the study (14.2%). The proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea groups). However, after applying the worst case scenario by assuming all withdrawn participants in the liraglutide group developed hypoglycaemia and all in sulphonylurea group did not develop hypoglycaemia, the direction of the result is reversed.
Incomplete outcome data (attrition bias) Body weight	Unclear risk	**Quote:** "The statistical evaluation followed the intention-to-treat principle, and subjects contributed to the evaluation "as randomised". " **Comment:** 50 participants withdrew from the study (14.2%). The proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea groups). However, it is unclear whether the direction of the results would change after applying the worst case scenario from the reported results of a mean decrease in body weight of -3.94 kg in favour of liraglutide, as there is no reliable, plausible magnitude of weight change that would constitute a reasonable estimate to be used in the worst case scenario.
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "The statistical evaluation followed the intention-to-treat principle, and subjects contributed to the evaluation "as randomised". " **Comment:** 50 participants withdrew from the study (14.2%). The proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea groups). However, after applying the worst case scenario by assuming all withdrawn participants in the liraglutide group were free from any adverse effects and all in the sulphonylurea group developed adverse effects, the direction of the result is reversed.
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** a large number of participants (50) withdrew from the study (14.2%). While the proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea group), the direction and impact of this dropout is unknown.

Azar 2016 *(Continued)*

Incomplete outcome data (attrition bias) Blood pressure	Unclear risk	**Comment:** a large number of participants (50) withdrew from the study (14.2%). While the proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea group), the direction and impact of this dropout is unknown.
Incomplete outcome data (attrition bias) Blood glucose	High risk	**Quote:** "The statistical evaluation followed the intention-to-treat principle, and subjects contributed to the evaluation “as randomised”. " **Comment:** 50 participants withdrew from the study (14.2%). The proportion of withdrawals was balanced between the two groups (26 from liraglutide and 24 from sulphonylurea group). However, we consider the current reported difference in fasting blood glucose reading of -1.8 mmol/L in favour of liraglutide to be too fragile to be preserved if a realistic worst case scenario is to be applied by assuming that withdrawn participants in the liraglutide group had consistently high glucose and those in the sulphonylurea group had consistently lower glucose values.
Selective reporting (reporting bias)	Low risk	**Comment:** all pre-specified outcomes were reported in sufficient detail
Other bias	Low risk	**Comment:** none identified

Belkhadir 1993

Study characteristics	
Methods	**Study design**: multi-centre, parallel randomised controlled trial
Participants	**Inclusion criteria**: people with type 2 diabetes, and treated with glibenclamide for at least 6 months **Exclusion criteria**: newly diagnosed people with diabetes and those whose response to glibenclamide was not yet known **Diagnostic criteria**: — **Setting**: clinics and hospital **Age group**: adults **Gender distribution**: 66:34 (females:males ratio) **Country where trial was performed**: Morocco
Interventions	**Intervention**: full dose of glibenclamide **Comparator**: reduced dose of glibenclamide (75% of normal daily dose) **Duration of intervention**: 4 weeks **Duration of follow-up**: 4 weeks **Run-in period**: 4 weeks **Number of trial centres**: 5 (2 university hospitals, 1 private hospital, 2 private clinics)
Outcomes	**Reported outcome(s) in full text of publication**: serum fructosamine, HbA1c, body weight and number of hypoglycaemic events
Study details	**Trial terminated early**: no

Belkhadir 1993 *(Continued)*

Publication details	**Language of publication**: English **Funding**: commercial funding (Hoechst AG) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "We have therefore conducted a randomised controlled trial of different treatment regimens in a group of patients with non-insulin dependent diabetes living in two Moroccan cities who were being treated with glibenclamide"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "patients, who had decided to fast, were randomised consecutively with sealed envelopes to one of two regimens." **Comment:** participants were "randomised consecutively with sealed envelopes" and no further details were given on the methods of sequence generation
Allocation concealment (selection bias)	Unclear risk	**Quote:** "patients, who had decided to fast, were randomised consecutively with sealed envelopes to one of two regimens." **Comment:** no further details were given to enable an assessment of the independence between random sequence generation and allocation. As it was not stated whether the envelopes were also opaque, we have rated the domain as unclear
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Patients' hypoglycaemic events were assessed retrospectively and rated on a six point scale." **Comment:** the study was not blinded as the two active groups compared had different glibenclamide doses, and the outcomes assessed included hypoglycaemic events
Blinding of participants and personnel (performance bias) Body weight	High risk	**Comment:** the study was not blinded as the two active groups compared had different glibenclamide doses. It was unclear who assessed the outcome of body weight
Blinding of participants and personnel (performance bias) Blood glucose	Unclear risk	**Comment:** the study was not blinded as the two active groups compared had different glibenclamide doses
Blinding of participants and personnel (performance bias) HbA1c	Unclear risk	**Comment:** the study was not blinded as the two active groups compared had different glibenclamide doses
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** outcomes were hypoglycaemic events assessed by patients themselves who were not blinded to their intervention status
Blinding of outcome assessment (detection bias)	Unclear risk	**Comment:** it was unclear who assessed this outcome as study protocol was unavailable

Belkhadir 1993 *(Continued)*

Body weight		
Blinding of outcome assessment (detection bias) Blood glucose	Unclear risk	**Comment:** It was unclear who assessed this outcome as study protocol was unavailable
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "542 out of 591 patients (91.7%) completed the study, and a further 62 patients from the 542 violated the protocol." **Comment:** the numbers of withdrawn participants were balanced across the three groups (17 from the control group, and 16 each from the two fasting groups). However, the direction of effect in this outcome was sensitive to the assumption of worst case scenario by assuming all withdrawn participants in the control group developed hypoglycaemia and all in the glibenclamide group did not
Incomplete outcome data (attrition bias) Body weight	Unclear risk	**Quote:** "542 out of 591 patients (91.7%) completed the study, and a further 62 patients from the 542 violated the protocol." **Comment:** the numbers of withdrawn participants were balanced across the three groups (17 from the control group, and 16 each from the two fasting groups). However, it is unclear whether the direction of the results would change after applying the worst case scenario from the reported results of a mean decrease in body weight of -3.5 kg in favour of glibenclamide (full dose vs control), as there is no reliable, plausible magnitude of weight change that would constitute a reasonable estimate to be used in the worst case scenario
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** the numbers of withdrawn participants were balanced across the three groups (17 from the control group, and 16 each from the two fasting groups)
Incomplete outcome data (attrition bias) Blood glucose	High risk	**Quote:** "542 out of 591 patients (91.7%) completed the study, and a further 62 patients from the 542 violated the protocol." **Comment:** the numbers of withdrawn participants were balanced across the three groups (17 from the control group, and 16 each from the two fasting groups). In the current reported results, we considered the difference in fructosamine concentration of 24 micromol/L as too fragile to be preserved when a worst case scenario is applied by assuming that withdrawn participants in the control group consistently had a lower fructosamine level and those in the glibenclamide group consistently had a higher value
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol available
Other bias	Low risk	**Comment:** none identified

Brady 2014

Study characteristics	
Methods	**Study design**: open-label, parallel randomised controlled trial

Brady 2014 *(Continued)*

Participants	**Inclusion criteria**: aged ≥ 18 years with established T2DM on a stable dose of metformin monotherapy or dual therapy of metformin plus a sulphonylurea or pioglitazone with a HbA1c between 6.5% and 12%, and an intention to fast during the holy month of Ramadan for a minimum of 10 consecutive days **Exclusion criteria**: females who were pregnant, breastfeeding or intended to become pregnant, terminal illness, impaired renal function (serum-creatinine ≥ 135 µmol/L for males and ≥ 110 µmol/L for females), impaired liver function (alanine transaminase (ALT) ≥ 2.5 times upper limit of normal), significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association (NYHA) class III and IV) at the discretion of the investigator, hepatitis B antigen or hepatitis C antibody-positive, recurrent major hypoglycaemia as judged by the investigator, severe irritable bowel disorder or previous history of pancreatitis **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 years and above **Gender distribution**: 36:64 (females:males ratio) **Country where trial was performed**: United Kingdom
Interventions	**Intervention**: liraglutide titrated to 1.2 mg/day **Comparators**: sulphonylurea (included gliclazide, glimepiride and glibenclamide) either daily or twice-daily depending on investigators preference **Duration of intervention**: 12 weeks **Duration of follow-up**: — **Run-in period**: 14 days **Number of trial centres**: 2 (Leicester and Birmingham)
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, weight, blood pressure, lipid levels, patient satisfaction, hypoglycaemic event, hyperglycaemic event, physical activity, adverse events
Study details	**Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk.) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "The aim of this study is to determine if the addition of liraglutide is more effective in achieving a composite endpoint of HbA1c < 7.0%, no weight gain with no severe hypoglycaemic events, 12 weeks post Ramadan in people with established T2DM compared with a sulphonylurea"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "The randomisation sequence was computer-generated with a block size of four by an independents statistician and stratified by site (Leicester/Birmingham), pre-study."

Brady 2014 *(Continued)*

		Comment: randomisation sequence was computer-generated with a block size of 4 by an independent statistician and stratified by site
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Randomization was revealed after the baseline measurements were recorded" **Comment:** open-label; randomisation sequence was revealed after baseline data were recorded
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide), with significant hypoglycaemic episodes requiring hospitalisation (of some subjectivity) being one of the outcomes
Blinding of participants and personnel (performance bias) Body weight	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of participants and personnel (performance bias) Blood pressure	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of participants and personnel (performance bias) Lipid level	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of participants and personnel (performance bias) Treatment satisfaction	High risk	**Comment:** although not clearly stated, blinding was highly unlikely, as the intervention group received an additional medication (liraglutide)
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Quote:** "These include a hypoglycaemia questionnaire that was completed by the study clinician which included questions around the frequency of hypoglycaemic episodes with differing severity. Self-reported hypoglycaemia was captured as participants were instructed to record their blood glucose levels approximately five times a day throughout the duration of the study and to record any self-reported hypoglycaemic events in a specially designed blood glucose monitoring diary provided to them." **Comment:** one of the outcomes of significant hypoglycaemic episodes was self-assessed by the participants, who knew their status
Blinding of outcome assessment (detection bias) Body weight	High risk	**Comment:** the outcome on body weight was self-assessed by the participants who knew their status of randomisation

Brady 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "Safety and tolerability were assessed by reviewing reported adverse events during the study. All adverse events were rated by the study site investigators for intensity and relationship to study drug." **Comment:** one of the outcomes was adverse events, but these were self-reported by participants who knew their status of randomisation
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory
Blinding of outcome assessment (detection bias) Blood pressure	Unclear risk	**Comment:** the study was an open-label design, but it was unclear who measured the blood pressure outcome
Blinding of outcome assessment (detection bias) Lipid levels	Low risk	**Comment:** although this was an open-label trial, the outcome of lipid levels was objectively measured and generated in a laboratory
Blinding of outcome assessment (detection bias) Treatment satisfaction	High risk	**Comment:** the outcome of treatment satisfaction was self-assessed by the participants who knew their status of randomisation
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "Follow-up data was available for 78 participants at 3 weeks post Ramadan and 70 participants 12 weeks post Ramadan" **Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) Body weight	High risk	**Quote:** "Follow-up data was available for 78 participants at 3 weeks post Ramadan and 70 participants 12 weeks post Ramadan" **Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "Follow-up data was available for 78 participants at 3 weeks post Ramadan and 67 participants 12 weeks post Ramadan" **Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) HbA1c	High risk	**Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) Blood pressure	Unclear risk	**Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) Lipid level	Unclear risk	**Comment:** although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Incomplete outcome data (attrition bias) Treatment satisfaction	High risk	**Quote:** "Follow-up data was available for 78 participants at 3 weeks post Ramadan and 67 participants 12 weeks post Ramadan"

Brady 2014 *(Continued)*

		Comment: although the intention-to-treat analysis results based on imputation did not differ substantially from the complete case analysis, the rate of non-completers was too high (22% at 3 weeks and 29% at 12 weeks)
Selective reporting (reporting bias)	Unclear risk	**Comment:** no study protocol was available
Other bias	Low risk	**Comment:** none identified

Hassanein 2014

Study characteristics	
Methods	**Study design**: multi-centre parallel randomised double-blind controlled trial
Participants	**Inclusion criteria**: age 18 years or older, body mass index 22 to 45 kg/m^2, HbA1c 8.5% or lower, T2DM treated with metformin (≥ 1500 mg daily) plus any SU (for ≥ 12 weeks and, for SU, also ≤ 3 years) and the intention to fast during Ramadan **Exclusion criteria**: patients with an acute metabolic condition (such as ketoacidosis), a current diagnosis of congestive heart failure (NYHA class III or IV), other significant cardiovascular history within 6 months, acute or chronic liver disease or abnormal liver tests (alanine transaminase or aspartate transaminase more than 3 times the upper limit of normal, or bilirubin (total) more than 2 times the upper limit of normal), or clinically significant renal dysfunction (estimated glomerular filtration rate by Modification of Diet in Renal Disease, 60 mL/minute/1.73 m^2) **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 and above **Gender distribution**: 53:47 (females:males ratio) **Countries where trial was performed**: 16 countries (Denmark, Egypt, Germany, Indonesia, Jordan, Lebanon, Kuwait, Malaysia, Russia, Saudi Arabia, Singapore, Spain, Tunisia, Turkey, United Arab Emirates, United Kingdom)
Interventions	**Intervention**: vildagliptin 50 mg twice-daily + metformin at dosage between 1500 and 2500 mg daily **Comparators**: gliclazide in multiples of 80 mg + metformin at dosage between 1500 and 2500 mg daily **Duration of intervention**: up to 12 weeks **Duration of follow-up**: minimum 4 weeks post Ramadan and up to 30 weeks **Run-in period**: up to 4 weeks **Number of trial centres**: 69 sites
Outcomes	**Reported outcomes in full text of publication**: HbA1c, weight, hypoglycaemic event, adverse events
Study details	**Trial identifier**: NCT01758380 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novartis)

Hassanein 2014 *(Continued)*

	Publication status: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "Several observational studies were conducted with vildagliptin in patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan, showing significantly lower incidences of hypoglycaemia with vildagliptin versus sulphonylureas, including gliclazide. It was of interest to complement the existing real-life evidence with data from a randomised, double-blind, clinical trial."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "After an up-to-4-week screening period, eligible patients were randomised using interactive response technology in a 1:1 ratio to receive either vildagliptin or gliclazide in a double-blind, double-dummy fashion". **Comment:** randomisation was done using interactive response technology
Allocation concealment (selection bias)	Low risk	**Quote:** "After an up-to-4-week screening period, eligible patients were randomised using interactive response technology in a 1:1 ratio to receive either vildagliptin or gliclazide in a double-blind, double-dummy fashion". **Comment:** randomisation was done using interactive response technology, which was concealed from investigators
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	Low risk	**Quote:** "After an up-to-4-week screening period, eligible patients were randomised using interactive response technology in a 1:1 ratio to receive either vildagliptin or gliclazide in a double-blind, double-dummy fashion". **Comment:** we consider the use of the term double-blind to include blinding of participants and personnel
Blinding of participants and personnel (performance bias) Body weight	Low risk	**Comment:** we consider the use of the term double-blind to include blinding of participants and personnel
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** we consider the use of the term double-blind to include blinding of participants and personnel
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment:** this is an objective outcome measure.
Blinding of participants and personnel (performance bias) HbA1c	Low risk	**Comment:** we consider the use of the term double-blind to include blinding of participants and personnel
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	Unclear risk	**Quote:** "Each patient was provided with a diary, for recording hypoglycemia-related symptoms and blood glucose levels, as well as a home glucose monitor. Patients were educated regarding hypoglycaemia symptoms and treatment and the use of the home glucose monitor."

Hassanein 2014 *(Continued)*

		Comment: while the participants who self-assessed the outcomes of symptomatic hypoglycaemia were blinded, it was unclear whether the assessors of the blood glucose reading were blinded to the participant allocation status
Blinding of outcome assessment (detection bias) Body weight	Unclear risk	**Comment:** while the participants who self-assessed the outcomes were blinded, it was unclear whether the assessors were blinded to the participant allocation status
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** while the participants who self-assessed the outcomes were blinded, it was unclear whether the assessors were blinded to the participant allocation status
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment:** the outcome was objectively measured and reported
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment**: the outcome was objectively measured and reported
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Comment:** although 86% of the participants completed the study, those who did not complete withdrew consent or developed adverse events including hypoglycaemia. The authors performed intention-to-treat analysis by including all participants with outcomes data where available. However, the number of withdrawals was too large for the results to withstand the worst case scenario, as the scenario would inverse the direction of the effect.
Incomplete outcome data (attrition bias) Body weight	High risk	**Comment:** although 86% of the participants completed the study, those who did not complete withdrew consent or developed adverse events. The authors performed intention-to-treat analysis by including all participants with outcome data where available. The number of withdrawals was balanced between groups (40 in vildagliptin group and 39 in gliclazide group). The difference between the two groups in the adjusted mean difference in the body weight during the period of the study (0.2 kg slightly in favour of vildagliptin) was considered too fragile to be preserved by assuming a worst case scenario on the likely weight of the missing participants
Incomplete outcome data (attrition bias) All-cause mortality	Unclear risk	**Comment:** although 86% of the participants completed the study, those who did not complete withdrew consent. Modified intention-to-treat analysis set was used (all exposed participants were analysed).
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Comment:** although 86% of the participants completed the study, those who did not complete withdrew consent or developed adverse events. The authors performed intention-to-treat analysis by including all participants with outcome data where available. Participants who developed adverse events and did not complete the study had their adverse events included in the outcome data for adverse events. The number of withdrawals was balanced between groups (40 in vildagliptin group and 39 in gliclazide group). The difference in the rate of adverse events of 7.9% in favour of vildagliptin was insufficient to withstand the assumption of a worst-case scenario by assuming that all missing participants in the vildagliptin group developed adverse events and all in the gliclazide group did not
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** although 86% of the participants completed the study, those who did not complete withdrew consent. Modified intention-to-treat analysis set was used (all exposed participants were analysed).

Hassanein 2014 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	**Comment:** not all secondary outcomes pre-specified in protocol reported in publication
Other bias	Low risk	**Comment:** none identified

Hassanein 2018

Study characteristics	
Methods	**Study design**: multi-centre, parallel, randomised, open-label study
Participants	**Inclusion criteria**: adult patients (≥ 18 years in India, Lebanon, Malaysia and South Africa, ≥ 19 years in Algeria) with T2DM and expressed willingness to fast during Ramadan, treated with any basal, pre- or self-mixed insulin ± oral antidiabetics for ≥ 90 days (included metformin, sulphonylureas, glinides, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, sodium-glucose co-transporter-2 inhibitors), with HbA1c levels between 7.0% and 10.0% and body mass index (BMI) ≤ 45.0kg/m^2 **Exclusion criteria**: hypersensitivity to trial products and high probability of an unsuccessful fasting from a medical perspective **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 and above **Gender distribution**: 57:43 (females:males ratio) **Countries where trial was performed**: 4 countries (Algeria, India, Lebanon, Malaysia and South Africa)
Interventions	**Intervention**: insulin degludec/insulin aspart + oral antidiabetics **Comparators**: biphasic insulin aspart 30 + oral antidiabetics **Duration of intervention**: 22 to 34 weeks **Duration of follow-up**: 30 days **Run-in period**: up to 2 weeks **Number of trial centres**: 27 sites
Outcomes	**Reported outcomes in full text of publication**: HbA1c, fructosamine levels, hypoglycaemic event, adverse events
Study details	**Trial identifier**: NCT02648217 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk A/S) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "to compare the efficacy and safety of IDegAsp with BIAsp 30 before, during and after Ramadan in patients with T2DM who fasted during Ramadan in Algeria, India, Lebanon, Malaysia and South Africa."

Hassanein 2018 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were randomised using an interactive response system with an allocation ratio of 1:1 to IDegAsp" **Comment:** randomisation was done using interactive response technology
Allocation concealment (selection bias)	Low risk	**Quote:** "Patients were randomised using an interactive response system with an allocation ratio of 1:1 to IDegAsp" **Comment:** randomisation was done using interactive response technology and unlikely that investigators or participant would know sequence beforehand
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "This phase 3, open-label, randomised, treat-to-target clinical trial was conducted" **Comment:** all participants knew their allocation and hypoglycaemia was self-reported based upon symptoms
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** all participants knew their allocation, and it was likely that adverse events were self-reported based upon symptoms
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment:** while all participants knew their allocation, this is an objective outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label trial in which the knowledge of allocation could have influenced the outcomes
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** hypoglycaemia was self-assessed by the participants, who knew their status of randomisation
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Comment:** adverse events were likely to be self-assessed by the participants, who knew their status of randomisation
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment:** open-label design with outcome measure unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory

Hassanein 2018 *(Continued)*

Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote**: "Fifteen patients withdrew from the trial, which resulted in 248 completers (121 completers in the IDegAsp arm and 127 completers in the BIAsp 30 arm)" **Comment:** intention-to-treat analysis results based on imputation and only a low number of dropouts (5.7%)
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** withdrawals and reasons for withdrawal were documented, did not differ substantially between intervention groups and did not appear to be related to health status. Modified intention-to-treat analysis set was used (all exposed participants were analysed). Missing observations were considered missing at random in all analyses.
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote**: "Fifteen patients withdrew from the trial, which resulted in 248 completers (121 completers in the IDegAsp arm and 127 completers in the BIAsp 30 arm)" **Comment:** intention-to-treat analysis results based on imputation and only a low number of dropouts (5.7%)
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Comment:** withdrawals and reasons for withdrawal were documented, did not differ substantially between intervention groups and did not appear to be related to health status. Modified intention-to-treat analysis set was used (all exposed participants were analysed). Missing observations were considered missing at random in all analyses.
Selective reporting (reporting bias)	Low risk	**Comment:** all primary and secondary outcomes reported as pre-specified in protocol
Other bias	Low risk	**Comment:** none identified

Hassanein 2019

Study characteristics	
Methods	**Study design**: multi-centre, parallel, randomised, open-label controlled trial
Participants	**Inclusion criteria**: participants with type 2 diabetes (diagnosed for 1 year) insufficiently controlled with sulphonylurea and + basal insulin (50% of the maximum allowed dose) ± one oral anti-diabetic drug who expressed the intention to fast during Ramadan and provided written informed consent **Exclusion criteria**: patients with a HbA1c of < 7.5% or > 10%, BMI < 20 kg/m^2, treated with basal insulin for less than 6 months, unstable prior anti-diabetic medication, previous treatment with short or rapid-acting insulin for the past 6 months, history of GLP-1 drug discontinuation, not willing to perform self-monitoring of glucose, history of diabetic ketoacidosis, any clinically significant abnormality identified on physical examination or vital signs at the time of screening, or any condition (including but not limited to acute pancreatitis, severe gastroparesis, severe renal impairment or end-stage renal disease) that could make implementation of the protocol or interpretation of the study results difficult or could preclude the safe participation of the patient in the protocol **Diagnostic criteria**: — **Setting**: — **Age group**: adults aged 18 and above **Gender distribution**: 55:45 (females:males ratio)

Hassanein 2019 *(Continued)*

	Countries where trial was performed: 5 countries (India, Israel, Kuwait, Lebanon, Turkey)
Interventions	**Intervention**: lixisenatide + basal insulin ± metformin **Comparators**: sulfonylurea + basal insulin ± metformin **Duration of intervention**: 12 to 20 weeks **Duration of follow-up**: none **Run-in period**: up to 2 weeks **Number of trial centres**: 16 sites
Outcomes	**Reported outcomes in full text of publication**: HbA1c, weight, hypoglycaemic event, adverse events
Study details	**Trial identifier**: NCT02941367 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Sanofi) **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "Adding lixisenatide to basal insulin (BI) instead of sulphonylurea (SU), versus continuing SU + BI was assessed in people with type 2 diabetes mellitus (T2DM) who intended to fast during Ramadan 2017."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Eligible participants were randomised 1:1 without stratification, according to a randomisation scheme provided by the study biostatistician, to receive BI ± existing metformin plus either open-label subcutaneous lixisenatide (identified with treatment kit numbers generated by Sanofi) or oral open-label SU (provided according to local regulations)." **Comment:** sequence randomisation was done centrally by a study biostatistician
Allocation concealment (selection bias)	Low risk	**Quote:** "The investigator/designee contacted the Interactive Response Technology for the participant number at screening and to allocate the treatment arm at randomisation." **Comment:** allocation was concealed from the investigators since they had to contact the interactive response system
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Body weight	Low risk	**Comment:** outcome was assessed during clinic visits by investigators

Hassanein 2019 *(Continued)*

Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** this was an open-label trial and participants were likely to self-report any adverse events
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label trial in which the knowledge of allocation could have influenced the outcomes
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** primary outcomes (occurrence of hypoglycaemic events) were reported by participants who were not blinded
Blinding of outcome assessment (detection bias) Body weight	Low risk	**Comment:** outcome was objective and measured during clinic visits
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Comment:** outcome was likely to be reported by participants who were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote:** "The intent-to-treat (ITT) population (efficacy endpoints) was defined as all randomised participants treated at least once with the study treatment and grouped according to randomisation assignment." **Comment:** only 5 participants discontinued the study prematurely and these were adjusted using the ITT analysis; 97.3% completed the trial
Incomplete outcome data (attrition bias) Body weight	Low risk	**Quote:** "The intent-to-treat (ITT) population (efficacy endpoints) was defined as all randomised participants treated at least once with the study treatment and grouped according to randomisation assignment." **Comment:** only 5 participants discontinued the study prematurely and these were adjusted using the ITT analysis; 97.3% completed the trial
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "The intent-to-treat (ITT) population (efficacy endpoints) was defined as all randomised participants treated at least once with the study treatment and grouped according to randomisation assignment." **Comment:** only 5 participants discontinued the study prematurely and these were adjusted using the ITT analysis; 97.3% completed the trial
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote: "**The intent-to-treat (ITT) population (efficacy endpoints) was defined as all randomised participants treated at least once with the study treatment and grouped according to randomisation assignment. **Comment:** only 5 participants discontinued the study prematurely and these were adjusted using the ITT analysis; 97.3% completed the trial
Selective reporting (reporting bias)	Unclear risk	**Comment:** while primary outcomes were presented clearly, there was a deviation in the reported secondary outcomes as not all secondary outcomes prespecified in the protocol were reported

Hassanein 2019 *(Continued)*

Other bias	Low risk	**Comment:** none identified

Lee 2015

Study characteristics	
Methods	**Study design**: open-label, parallel randomised controlled trial
Participants	**Inclusion criteria**: diagnosed with type 2 diabetes, aged 18 to 75 years, with an HbA1c of 58 to 97 mmol/mol (7.5% to 11%), and willing to fast for at least 15 days, had Internet access, an email address or a smartphone, and provided informed consent **Exclusion criteria**: those who were unable or unwilling to give informed consent or communicate with local study staff, current diagnosis of schizophrenia, other psychotic disorders or bipolar disorder Hospitalisation for depression in past 6 months, plans to relocate to an area or travel plans that do not permit full participation in the study, lack of support from primary health care provider or family members History of bariatric surgery, small bowel resection, or extensive bowel resection, currently pregnant or nursing history of cancer requiring treatment in the past five years, except for non-melanoma skin cancers or cancers that have clearly been cured or in the opinion of the investigator carry an excellent prognosis (e.g. stage 1 cervical cancer), history of cardiovascular disease (heart attack or procedure within the past three months or participation in a cardiac rehabilitation programme within last 3 months, stroke or history/treatment for transient ischaemic attacks in the past 3 months, or documented history of pulmonary embolus in past 6 months) and other medical, psychiatric or behavioural factors that in the judgement of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol **Diagnostic criteria**: — **Setting**: outpatient **Age group**: adults aged between 18 and 75 years old **Gender distribution**: 57:43 (females:males ratio) **Country where trial was performed**: Malaysia
Interventions	**Intervention**: telemonitoring with Ramadan-focused education **Comparator**: Ramadan-focused education **Duration of intervention**: up to 6 weeks **Duration of follow-up**: — **Run-in period**: 1 week **Number of trial centres**: —
Outcomes	**Reported outcome(s) in full text of publication**: blood glucose, lipid, hypoglycaemic event
Study details	**Trial identifier**: NCT02189135 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: non-commercial funding (SEGi University and Monash University Malaysia)

Lee 2015 *(Continued)*

	Publication status: short original article in a peer-reviewed journal
Stated aim for study	**Quote**: "The objective of this study was to examine the effects of a telemonitoring programme for Muslims with Type 2 diabetes who were fasting during Ramadan."
Notes	Poor quality of reporting in study. Study authors contacted for clarification.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** study authors were contacted, and replied that the cluster-randomisation was performed centrally by a senior author who acted as the statistician
Allocation concealment (selection bias)	Low risk	**Comment:** "all patient baseline assessments in the practice were completed before allocation was revealed."
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Comment:** not stated, but blinding appeared highly unlikely as one group received telemonitoring and another Ramadan-focused pre-education
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Comment:** while this was a cluster-randomised study, participants were not blinded to treatment allocation
Blinding of participants and personnel (performance bias) Lipid level	Unclear risk	**Comment:** not stated, but blinding appeared highly unlikely as one group received telemonitoring and another Ramadan-focused pre-education
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** part of the outcome was self-reported by participants who were highly unlikely to have been blinded
Blinding of outcome assessment (detection bias) Blood glucose	High risk	**Comment:** blood glucose was measured in an independent laboratory based upon samples taken during clinic visits by investigators
Blinding of outcome assessment (detection bias) Lipid levels	Low risk	**Comment:** blood lipids and triglyceride levels were measured in an independent laboratory based upon samples taken during clinic visits by investigators
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "32 out of 37 participants (86%) completed the study." **Comment:** the authors did not perform imputation for missing data, thus with the small sample size and high attrition, this would have impacted the event rates leading to false-positive results
Incomplete outcome data (attrition bias) Blood glucose	High risk	**Quote:** "32 out of 37 participants (86%) completed the study." **Comment:** the authors did not perform imputation for missing data, thus the small sample size and high attrition would have resulted in incorrect conclusions
Incomplete outcome data (attrition bias)	High risk	**Quote:** "32 out of 37 participants (86%) completed the study."

Lee 2015 *(Continued)*

Lipid level		**Comment:** the authors did not perform imputation for missing data, thus the small sample size and high attrition would have impacted the event rates leading to false-positive results
Selective reporting (reporting bias)	High risk	**Comment:** major clinical outcomes of hypoglycaemic episodes were presented as total number of episodes rather than total number of participants with the episode; not all secondary outcomes pre-specified in protocol were reported
Other bias	Low risk	**Comment:** none identified

Lee 2017a

Study characteristics	
Methods	**Study design**: open-label, parallel, cluster-randomised controlled trial
Participants	**Inclusion criteria**: diagnosed with type 2 diabetes, aged 18 to 75 years, with an HbA1c of 58 to 97 mmol/mol (7.5% to 11%) and willing to fast for at least 15 days, had Internet access, an email address or a smartphone, and provided informed consent **Exclusion criteria**: those who were unable or unwilling to give informed consent or communicate with local study staff, current diagnosis of schizophrenia, other psychotic disorders or bipolar disorder Hospitalisation for depression in past 6 months, plans to relocate to an area or travel plans that do not permit full participation in the study, lack of support from primary health care provider or family members History of bariatric surgery, small bowel resection or extensive bowel resection, currently pregnant or nursing history of cancer requiring treatment in the past 5 years, except for non-melanoma skin cancers or cancers that have clearly been cured or in the opinion of the investigator carry an excellent prognosis (e.g. stage 1 cervical cancer), history of cardiovascular disease (heart attack or procedure within the past 3 months or participation in a cardiac rehabilitation programme within last 3 months, stroke or history/treatment for transient ischaemic attacks in the past 3 months or documented history of pulmonary embolus in past 6 months) and other medical, psychiatric or behavioural factors that in the judgement of the Principal Investigator may interfere with study participation or the ability to follow the intervention protocol **Diagnostic criteria**: — **Setting**: outpatient **Age group**: adults aged between 18 and 75 years old **Gender distribution**: 53:47 (females:males ratio) **Country where trial was performed**: Malaysia
Interventions	**Intervention**: telemonitoring with Ramadan-focused education **Comparator**: Ramadan-focused education **Duration of intervention**: 12 weeks **Duration of follow-up**: — **Run-in period**: — **Number of trial centres**: 11

Lee 2017a *(Continued)*

Outcomes	**Reported outcome(s) in full text of publication**: blood glucose, lipid**,** hypoglycaemic event, body mass index
Study details	**Trial identifier**: NCT02189135 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: non-commercial funding (SEGi University, Monash University Malaysia and Ministry of Science, Technology and Innovation Malaysia) **Publication status**: short original article in a peer-reviewed journal
Stated aim for study	**Quote**: "In this study, we examine the effects of a telemedicine program on patients fasting during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "A researcher, independent of the study team, conducted the cluster randomisation and allocated clinics to telemonitoring intervention (TG) or usual care (UC) group using a centrally administered treatment code." **Comment:** independent team who conducted the randomisation and sequence generation
Allocation concealment (selection bias)	Low risk	**Quote:** "A researcher, independent of the study team, conducted the cluster randomisation and allocated clinics to telemonitoring intervention (TG) or usual care (UC) group using a centrally administered treatment code." **Comment:** independent team who performed and conducted the cluster-randomisation
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups with self-reported symptoms of hypoglycaemia included as an outcome
Blinding of participants and personnel (performance bias) Body weight	Low risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups, but body weight was measured during clinic visits by investigators
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** authors were contacted for clarification and reported that there were no adverse events besides hypoglycaemia
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups and the outcome of blood glucose was self-reported

Lee 2017a *(Continued)*

Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups and the outcome of quality of life was self-reported
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups, which might have led to differences in other aspects of diabetes care that might have resulted in differences in the outcome
Blinding of participants and personnel (performance bias) Blood pressure	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups, which might have led to differences in other aspects of diabetes care that might have resulted in differences in the outcome
Blinding of participants and personnel (performance bias) Lipid level	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups, which might have led to differences in other aspects of diabetes care that might have resulted in differences in the outcome
Blinding of participants and personnel (performance bias) Self-care behaviour	High risk	**Comment:** blinding appeared highly unlikely as the intervention differed between groups, which might have led to differences in other aspects of diabetes care that might have resulted in differences in the outcome, which was self-reported
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** self-reported symptoms of hypoglycaemia were included as an outcome with participants who were highly unlikely to have been blinded
Blinding of outcome assessment (detection bias) Body weight	Unclear risk	**Comment:** body weight and body mass index were included as an outcome and calculated by investigators
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Comment:** authors were contacted for clarification, who reported that there were no adverse events besides hypoglycaemia
Blinding of outcome assessment (detection bias) Blood glucose	Low risk	**Comment:** blood glucose and HbA1c were measured in an independent laboratory based upon samples taken during clinic visits by investigators
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Comment:** outcome was self-reported by participants who were unblinded
Blinding of outcome assessment (detection bias) HbA1c	Low risk	An objective outcome measured in a laboratory with results generated automatically
Blinding of outcome assessment (detection bias) Blood pressure	Unclear risk	**Comment:** this was an open-label study. The knowledge of the intervention assignment might have influenced concomitant care and outcomes.
Blinding of outcome assessment (detection bias)	Low risk	An objective outcome measured in a laboratory with results generated automatically

Lee 2017a *(Continued)*
Lipid levels

Blinding of outcome assessment (detection bias) Self-care behaviour	High risk	Self-reported outcome from participants who were very unlikely to have been blinded
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Body weight	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) HbA1c	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain
Incomplete outcome data (attrition bias) Blood pressure	High risk	**Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Blood glucose	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random"

Lee 2017a *(Continued)*

		Comment: it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Lipid level	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Incomplete outcome data (attrition bias) Self-care behaviour	High risk	**Quote:** "All data were analysed based upon an intention-to-treat basis using a complete case analysis with the assumption that missing outcomes are missing at random" **Comment:** it is unclear from the statement above what the authors meant by complete case analysis, although it appeared that data from missing participants were not imputed. Based on the absolute rate of missing data (23%), the study is considered as high-risk in this domain.
Selective reporting (reporting bias)	High risk	**Comment:** there were changes between outcomes pre-specified in the protocol and publication
Other bias	Unclear risk	**Comment:** there is an unclear risk for recruitment bias. The clusters in the study were clinics, where ongoing patients were recruited to undergo the designated intervention after the initial cluster-randomisation took place. It was unclear whether there was any preferential recruitment of patients into any clusters by the investigators from knowledge of the designated intervention by the clinic.

Lum 2018

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: all Muslim people over 21 years of age with type 2 diabetes who plan to fast for at least 10 days during the month of Ramadan **Exclusion criteria**: those with history of recurrent hypoglycaemia, who are pregnant, eGFR < 30 mL/min 3 months prior to Ramadan, HbA1c > 9.5%, with diabetes mellitus-related admission 1 month prior to Ramadan, on active short-term corticosteroid treatment, and those who are unable to complete the questionnaires **Diagnostic criteria**: — **Setting**: primary care institution and tertiary hospital **Age group**: adults aged 21 years and above **Gender distribution**: 68: 32 (females:males ratio) **Country where trial was performed**: Singapore
Interventions	**Intervention**: collaborative algorithm for individuals with type 2 diabetes during Ramadan (FAST) which included education, self-monitoring of blood glucose and dosage adjustment/modification

Lum 2018 *(Continued)*

	Comparator: usual care **Duration of intervention**: — **Duration of follow-up**: — **Run-in period**: — **Number of trial centres**: —
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, blood glucose, hypoglycaemic episode
Study details	**Trial identifier:** NCT03314246 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**:non-commercial funding (Ministry of Education Singapore) **Publication status**: brief report in a peer-reviewed journal
Stated aim for study	**Quote**: "to develop and evaluate an evidence-based collaborative clinical algorithm that incorporated elements of empowerment."
Notes	Poor quality of reporting as study duration period was unclear, no demographics of participants were provided and unclear primary outcome. Author contacted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Eligible individuals were randomised into the intervention group (use of FAST) or the control group (usual care without use of FAST)." **Comment:** no further information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Eligible individuals were randomised into the intervention group (use of FAST) or the control group (usual care without use of FAST)." **Comment:** no further information on random sequence generation or allocation concealment
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "FAST was developed into an epistemic tool with four components: screening, education, dose modification by healthcare provider, and dose adjustment through SMBG." **Comment:** blinding appeared highly unlikely as the intervention group was treated according to a collaborative clinical algorithm while the control group received usual care
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Quote:** "FAST was developed into an epistemic tool with four components: screening, education, dose modification by healthcare provider, and dose adjustment through SMBG." **Comment:** blinding appeared highly unlikely as the intervention group was treated according to a collaborative clinical algorithm while the control group received usual care. This outcome is likely to be self-reported during clinic visits, during which investigators would have made any necessary changes to medication dosage

Lum 2018 *(Continued)*

Blinding of participants and personnel (performance bias) HbA1c	High risk	**Quote:** "FAST was developed into an epistemic tool with four components: screening, education, dose modification by healthcare provider, and dose adjustment through SMBG." **Comment:** blinding appeared highly unlikely as the intervention group was treated according to a collaborative clinical algorithm while the control group received usual care. Non-blinding might have influenced aspects of care and outcome.
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** there was no mention of blinding of outcome assessors. However, the outcome was self-reported (occurrence of major and minor hypoglycaemic events)
Blinding of outcome assessment (detection bias) Blood glucose	Unclear risk	**Comment:** there was no mention of blinding of outcome assessors. However, these outcomes were objective laboratory outcomes (HbA1c, FBG and PPG)
Blinding of outcome assessment (detection bias) HbA1c	Low risk	This is an objective outcome measured in a laboratory with automatically generated results
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Unclear risk	**Comment:** no information on missing data
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** no information was available on missing data
Incomplete outcome data (attrition bias) Blood glucose	Unclear risk	**Comment:** no information on missing data
Selective reporting (reporting bias)	High risk	**Comment:** most pre-specified secondary outcomes listed in the trial register were not reported
Other bias	Low risk	**Comment:** none identified

Mafauzy 2002

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: Muslims with type 2 diabetes who practised Ramadan fasting, treated with SU (either alone or in combination with metformin or acarbose) for at least 6 months **Exclusion criteria**: patients with history of cardiac disease (congestive heart failure, angina pectoris, previous myocardial infarction); impaired kidney or liver function; severe uncontrolled hypertension, severe diabetic complications; or had received therapy with insulin, other investigational drugs and corticosteroids within the 6 months, patients with known unawareness of hypoglycaemic symptoms and those who were expected to break fast for more than 3 days during Ramadan **Diagnostic criteria**: WHO criteria **Setting**: —

Mafauzy 2002 *(Continued)*

	Age group: —
	Gender distribution: 28:72 (females:males ratio)
	Countries where trial was performed: 5 (Malaysia, United Kingdom, France, Saudi Arabia and Morocco)
Interventions	**Intervention**: repaglinide
	Comparator: glibenclamide
	Duration of intervention: 14 weeks
	Duration of follow-up: —
	Run-in period: 6 weeks
	Number of trial centres: 18 study centres (5 centres in Malaysia, 4 in the UK, 5 in France, 3 in Saudi Arabia and 1 in Morocco)
Outcomes	**Reported outcome(s) in full text of publication**: serum fructosamine, blood glucose, HbA1c, hypoglycaemic event, adverse events
Study details	**Trial terminated early**: no
Publication details	**Language of publication**: English
	Funding: commercial funding (Novo Nordisk)
	Publication status: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "The purpose of this study was to compare glycaemic control in Muslim type 2 diabetic patients treated with repaglinide or glibenclamide during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "At their second visit (visit 2, week 0), patients were randomised to receive treatment with either repaglinide or glibenclamide administered orally as opaque gelatine capsules." **Comment:** no further information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Quote:** "At their second visit (visit 2, week 0), patients were randomised to receive treatment with either repaglinide or glibenclamide administered orally as opaque gelatine capsules." **Comment:** no further information on random sequence generation or allocation concealment
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "patients were requested to record blood glucose concentration during any symptomatic hypoglycaemic episode after visit 2." **Comment:** this was an open-label study. However, all efficacy measures (including hypoglycaemic events) were based on objective blood glucose readings. Some of the safety assessments were possibly self-reported by the participants

Mafauzy 2002 *(Continued)*

Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "The investigators recorded all adverse events experienced by patients throughout the study." **Comment:** this was an open-label study. The safety assessments were possibly self-reported by the participants
Blinding of participants and personnel (performance bias) Blood glucose	Low risk	**Quote:** "Blood samples to determine this concentration were collected at the start and end of Ramadan (visits 5 and 7)..." **Comment:** this outcome was assessed by the investigators based upon blood glucose readings obtained during clinic visits
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label study. The knowledge of the intervention assignment might have influenced concomitant care and outcomes.
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** it was not stated whether the assessors of the blood glucose reading and safety assessments were blinded to the patient allocation status. However, it is likely that the rates of hypoglycaemic episodes would be self-reported by the participants
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "The investigators recorded all adverse events experienced by patients throughout the study." **Comment:** they were vital signs, 12-LEA ECG, haematological, biochemical and laboratory assessments. It was unclear if the outcome assessors were blinded but given the nature of the measurements, they were not likely biased by lack of blinding.
Blinding of outcome assessment (detection bias) Blood glucose	High risk	**Comment:** participants were requested to record blood glucose concentration during any symptomatic episode and midday blood glucose concentrations during Ramadan in their patient diaries. These data were then transformed to record forms at the study centres.
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment**: the outcome was objectively measured and reported
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "A total of 235 patients were randomised and received repaglinide (116 patients) or glibenclamide (119 patients). One hundred and ninety-seven (84%) patients completed the trial in accordance with the protocol. The reasons for discontinuation were non-compliance with protocol (16 patients), withdrawals due to adverse events (six patients), ineffective therapy (ten patients) and other reasons (six patients)." **Comment:** the number of participants with non-compliance with protocol was high
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	High risk	**Quote:** "A total of 235 patients were randomised and received repaglinide (116 patients) or glibenclamide (119 patients). One hundred and ninety-seven (84%) patients completed the trial in accordance with the protocol. The reasons for discontinuation were non-compliance with protocol (16 patients), withdrawals due to adverse events (six patients), ineffective therapy (ten patients) and other reasons (six patients)." **Comment:** the number of participants with non-compliance with protocol was high

Mafauzy 2002 *(Continued)*

Incomplete outcome data (attrition bias) HbA1c	High risk	**Quote:** "A total of 235 patients were randomised and received repaglinide (116 patients) or glibenclamide (119 patients). One hundred and ninety-seven (84%) patients completed the trial in accordance with the protocol. The reasons for discontinuation were non-compliance with protocol (16 patients), withdrawals due to adverse events (six patients), ineffective therapy (ten patients) and other reasons (six patients)." **Comment:** the number of participants with non-compliance with protocol was high
Incomplete outcome data (attrition bias) Blood glucose	Unclear risk	**Quote:** "A total of 235 patients were randomised and received repaglinide (116 patients) or glibenclamide (119 patients). One hundred and ninety-seven (84%) patients completed the trial in accordance with the protocol. The reasons for discontinuation were non-compliance with protocol (16 patients), withdrawals due to adverse events (six patients), ineffective therapy (ten patients) and other reasons (six patients)." **Comment:** the number of participants with non-compliance with protocol was high
Selective reporting (reporting bias)	High risk	**Comment:** the major efficacy outcomes specified in the methods of the study and expected of this study were reported in sufficient detail. However, there is insufficient detail reported on adverse events. Also, nothing was reported on the other safely assessments including vital signs, 12-lead ECG and various laboratory, blood and biochemical outcomes. No study protocol was available.
Other bias	Low risk	**Comment:** none identified

Mahla 2014

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: adult patients with type 2 diabetes who were insulin-naive, no history of ketoacidosis, intend to fast for Ramadan willingly and had been on a combination therapy of metformin and sulphonylurea for at least 6 months, body mass index (BMI) greater than 25 and less than 40 kg/m^2 and haemoglobin A1c (HbA1c) greater than 6.5% **Exclusion criteria**: — **Diagnostic criteria**: — **Setting**: — **Age group**: adult patients **Gender distribution**: — **Country/countries where trial was performed**: —
Interventions	**Intervention**: vildagliptin 50 mg twice daily with metformin **Comparator**: long-acting sulphonylurea medication regimen (glimepiride or gliclazide) with metformin **Duration of intervention**: 2 months **Duration of follow-up**: 1 month

Mahla 2014 *(Continued)*

	Run-in period: —
	Number of trial centres: —
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, hypoglycaemic event, body mass index, adverse events
Study details	**Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novartis) **Publication status**: full original article of a peer-reviewed journal
Stated aim for study	**Quote**: "To study the incidence of hypoglycaemia, glycaemic control and body weight changes in patients with type 2 diabetes treated with vildagliptin and metformin versus another group treated with sulphonylureas and metformin during and after the period of fasting in Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The study is an interventional, randomised open label clinical trial." **Comment:** no further information provided on random sequence generation
Allocation concealment (selection bias)	Unclear risk	**Quote:** "The study is an interventional, randomised open label clinical trial." **Comment:** no further information provided on random sequence generation and allocation concealment
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Hypoglycemia was defined based on symptoms of hypoglycaemia that improved with sugar intake or any value less than 70 mg/dl recorded by self glucose monitoring." **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Body weight	High risk	**Comment:** this was an open-label trial with self-reported outcome. Patients were not blinded to allocation
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Comment:** this was an open-label trial with self-reported outcome. Patients were not blinded to allocation
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label trial in which participants were not blinded to allocation. The knowledge of intervention allocation could have influenced the concomitant care during the study and influenced the outcome.
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** this was unclear. In addition to objective laboratory outcomes, a self-reported outcome (occurrence of hypoglycaemic events) was possibly included with participants who were not blinded

Mahla 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Body weight	High risk	**Comment:** unclear if investigators were blinded to outcomes assessment, but participants were not blinded
Blinding of outcome assessment (detection bias) Blood glucose	Low risk	**Comment:** unclear if investigators were blinded to outcomes assessment, but participants were not blinded. However, outcome was objective and results were generated in a laboratory.
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** unclear if investigators were blinded to outcomes assessment, but participants were not blinded. However, outcome was objective and results were generated in a laboratory.
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	High risk	**Quote:** "The dropout rate was around 36% as 25 patients did not complete the study. The main reasons for dropping out were as follows: the patient stopped fasting because of a loss of interest in the study without any medical reason (seven patients: three in the study group and four in the control group); the patient was travelling (five patients: three in the study group and two in the control group); the patient developed a medical condition that prevented fasting (nephrolithiasis, deep venous thrombosis and thyroidectomy) (three patients: two in the study group and one in the control group; one patient in the control group took a drug that was non compatible with the protocol." **Comment:** although the reasons for non-completion are described clearly, and are comparable between the groups, the percentage is too high (36%)
Incomplete outcome data (attrition bias) Body weight	High risk	**Quote:** "The dropout rate was around 36% as 25 patients did not complete the study. The main reasons for dropping out were as follows: the patient stopped fasting because of a loss of interest in the study without any medical reason (seven patients: three in the study group and four in the control group); the patient was travelling (five patients: three in the study group and two in the control group); the patient developed a medical condition that prevented fasting (nephrolithiasis, deep venous thrombosis and thyroidectomy) (three patients: two in the study group and one in the control group; one patient in the control group took a drug that was non compatible with the protocol." **Comment:** although the reasons for non-completion are described clearly, and are comparable between the groups, the percentage is too high (36%)
Incomplete outcome data (attrition bias) HbA1c	High risk	**Comment:** the high dropout rate of 36% posed a high risk of bias in this domain
Incomplete outcome data (attrition bias) Blood glucose	High risk	**Quote:** "The dropout rate was around 36% as 25 patients did not complete the study. The main reasons for dropping out were as follows: the patient stopped fasting because of a loss of interest in the study without any medical reason (seven patients: three in the study group and four in the control group); the patient was travelling (five patients: three in the study group and two in the control group); the patient developed a medical condition that prevented fasting (nephrolithiasis, deep venous thrombosis and thyroidectomy) (three patients: two in the study group and one in the control group; one patient in the control group took a drug that was non compatible with the protocol." **Comment:** although the reasons for non-completion are described clearly, and are comparable between the groups, the percentage is too high (36%)
Selective reporting (reporting bias)	Unclear risk	**Comment:** no protocol available. Authors contacted for further clarification but declined to provide details
Other bias	Low risk	**Comment:** none identified

Shehadeh 2015

Study characteristics	
Methods	**Study design**: parallel, cluster-randomised controlled trial
Participants	**Inclusion criteria**: adults > 18 years, with a diagnosis of type 2 diabetes and treated with insulin (premix preparations or basal and rapid-acting insulin) with or without metformin and/or a sulphonylurea drug for at least 3 months, have a HbA1c ≤ 10% in the past 3 months prior to enrolment, signed an informed consent form, and be capable and willing to perform self-measured blood glucose (SMBG) monitoring and use a patient diary as required **Exclusion criteria**: adults with type 1 diabetes, hypoglycaemia unawareness, hypersensitivity to levemir or NovoMix 70, creatinine > 2.5 mg/L, AST and or ALT > 1.5 times the upper limit, were pregnant, or were mentally incapable, unwilling or had language barriers precluding adequate understanding of the study protocol or co-operation **Diagnostic criteria**: — **Setting**: primary care clinic **Age group**: adults **Gender distribution**: 62:38 (females:males ratio) **Country where trial was performed**: Israel
Interventions	**Intervention**: levemir and NovoMix 70 **Comparator**: standard care according to the American Diabetes Association recommendation **Duration of intervention**: 30 days **Duration of follow-up**: — **Run-in period**: 2 to 4 weeks **Number of trial centres**: 12
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, hypoglycaemic events, blood glucose, blood lipids, adverse events
Study details	**Trial identifier**: NCT01354925. **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (Novo Nordisk) **Publication status**: full text in a peer-reviewed journal
Stated aim for study	**Quote**: "assessed the effect of a new structured insulin protocol containing detemir (levemir) and a biphasic insulin (NovoMix 70), in patients with type 2 diabetes treated previously with insulin, who fasted during the Ramadan and compared the effect of this new protocol to standard car."
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Shehadeh 2015 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	**Quote:** "Six pairs of clinics were matched for mean patients' age, and clinic size. Thereafter matched clinics were randomly selected for the interventional arm or the control arm of the study." **Comment:** no further information on random sequence generation for cluster assignment
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Six pairs of clinics were matched for mean patients' age, and clinic size. Thereafter matched clinics were randomly selected for the interventional arm or the control arm of the study." **Comment:** no further information on random sequence generation and allocation concealment for cluster assignment
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** this was an open-label trial where adverse events were possibly self-reported by the participants
Blinding of participants and personnel (performance bias) Blood glucose	High risk	**Comment:** this was an open-label trial where participants reported their blood glucose levels
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Comment:** this was an open-label trial with self-reported, subjective outcome that could have been influenced by knowledge of the allocation
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label trial in which all outcomes could have been influenced by knowledge of the allocation
Blinding of participants and personnel (performance bias) Lipid level	High risk	**Comment:** this was an open-label trial in which all outcomes could have been influenced by knowledge of the allocation
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Quote:** "Glucose measurements was self-performed four times daily (4-point SMBG) beginning on the first trial day: at dawn up to 60 min before Suhor, between noon and 2 pm hours, at the evening up to 60 min before Eftar, and 2–3 hr after Eftar. All blood glucose levels were recorded by patients in a personal diary." **Comment:** 4-point SMBG recorded by patients who were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** it was unclear if the assessor of the other objective measures was blinded but unlikely given the open-label design

Shehadeh 2015 *(Continued)*

Blinding of outcome assessment (detection bias) Blood glucose	High risk	**Quote:** "Glucose measurements was self-performed four times daily (4-point SMBG) beginning on the first trial day: at dawn up to 60 min before Suhor, between noon and 2 pm hours, at the evening up to 60 min before Eftar, and 2–3 hr after Eftar. All blood glucose levels were recorded by patients in a personal diary." **Comment:** 4-point SMBG recorded by participants who were not blinded to treatment allocation
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Comment:** this was an open-label trial with self-reported, subjective outcome
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and auto-generated in a laboratory
Blinding of outcome assessment (detection bias) Lipid levels	Low risk	**Comment:** although this was an open-label trial, the outcome of lipid levels was objectively measured and auto-generated in a laboratory
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Incomplete outcome data (attrition bias) HbA1c	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia

Shehadeh 2015 *(Continued)*

		or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Incomplete outcome data (attrition bias) Blood glucose	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated. ." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Incomplete outcome data (attrition bias) Lipid level	Low risk	**Quote:** "124/127 patients completed the study in the intervention group and 114/118 patients completed the study in the control group, and these patients were included in the per protocol analyses. Patients were withdrawn from the study at any time if he or she wished to do so, or when severe hypoglycaemia or hyperglycaemia occurred that required hospitalisation, or if the study's physician thought it was indicated." **Comment:** although the exact reasons for the dropout at the end of the study were not specified, the number was small and comparable between the two groups (2.9%)
Selective reporting (reporting bias)	High risk	**Comment:** there was major deviation in terms of listed outcomes in the trial register and those reported in the publication. Only the primary outcome was listed in the trial register while the publication listed outcomes including changes in HbA1c, SMBG, fructosamine, occurrence of hypoglycaemic and hyperglycaemic episodes, and adverse events.
Other bias	Unclear risk	**Comment:** Additional consideration for a cluster-randomised trial: 1. There is an unclear risk of recruitment bias. The clusters in the study were clinics, where ongoing patients were recruited to undergo the designated intervention after the initial cluster-randomisation took place. It was unclear whether there was any preferential recruitment of patients into any cluster by the investigators from knowledge of the designated intervention by the clinic. 2. There is a low risk of unit of analysis error, as the study accounted for the effect of clustering in the analysis using mixed models. Overall, due to the presence of an unclear risk among those domains specifically for cluster-RCTs, a rating of unclear risk is given under 'Other bias'.

Wan Seman 2016

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: people with type 2 diabetes mellitus, aged 18 to 65 years, who intended to fast during Ramadan, glycated haemoglobin (HbA1c) levels of 7% to 10.5%, who were treated with stable doses of sulphonylurea (glimepiride, gliclazide or glibenclamide) and metformin (> 1500 mg per day) during the 60 days before screening

Wan Seman 2016 *(Continued)*

	Exclusion criteria: people who were pregnant or breastfeeding as well as those who had impaired renal function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), recurrent urinary tract infections, alanine transaminase levels > 2.5 times the upper normal limit, malignancy, cardiovascular events within the last 90 days, or contraindication for fasting **Diagnostic criteria**: — **Setting**: primary care clinics and endocrine clinics in hospitals **Age group**: adults aged 18 to 65 years old **Gender distribution**: 40:60 (females:males ratio) **Country where trial was performed**: Malaysia
Interventions	**Intervention**: dapagliflozin with metformin **Comparators**: sulphonylurea (glimepiride, gliclazide or glibenclamide) and metformin **Duration of intervention**: 6 weeks **Duration of follow-up**: 6 weeks **Run-in period**: up to 6 weeks **Number of trial centres**: —
Outcomes	**Reported outcome(s) in full text of publication**: HbA1c, hypoglycaemic events, blood glucose, adverse events
Study details	**Trial identifier**: — **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial funding (AstraZeneca) **Publication status**: research letter in a peer-reviewed journal
Stated aim for study	**Quote**: "The aim of the present study was to assess the risk of hypoglycaemia associated with the use of dapagliflozin compared with that of sulphonylurea in patients with T2DM who fast during Ramadan."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomised at a 1:1 ratio using a 'blocked' randomisation protocol." **Comment:** sequence generation was generated using a blocked randomisation protocol but insufficient information to make judgement
Allocation concealment (selection bias)	Unclear risk	**Quote:** "Patients were randomised at a 1:1 ratio using a 'blocked' randomisation protocol." **Comment:** no information on allocation concealment

Wan Seman 2016 *(Continued)*

Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "Reported symptomatic hypoglycaemia was defined as typical hypoglycaemia symptoms not accompanied by plasma glucose determination" **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	High risk	**Comment:** this was an open-label trial where adverse events were possibly self-reported by the participants
Blinding of participants and personnel (performance bias) Blood glucose	Unclear risk	**Comment:** this was an open-label trial in which the knowledge of allocation could have influenced the outcomes
Blinding of participants and personnel (performance bias) HbA1c	High risk	**Comment:** this was an open-label trial in which the knowledge of allocation could have influenced the outcomes
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** it was not clearly stated in the article but the primary outcomes (occurrence of hypoglycaemic events) were reported by participants who were not blinded
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Comment:** this was not clearly stated in the article, but the outcome was reported by participants who were not blinded
Blinding of outcome assessment (detection bias) Blood glucose	Unclear risk	**Comment:** it was not clearly stated in the article if the assessors were blinded to these outcomes
Blinding of outcome assessment (detection bias) HbA1c	Low risk	**Comment:** although this was an open-label trial, the outcome of HbA1c was objectively measured and generated in a laboratory
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Unclear risk	**Comment:** dropout rate was 7.6% at 4 weeks follow-up. All reasons for dropout were well described and valid. However, there seem to be higher dropouts in the intervention group (83% vs 93% completing the study)
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Unclear risk	**Comment:** dropout rate was 7.6% at 4 weeks follow-up. All reasons for dropout were well described and valid. However, there seem to be higher dropouts in the intervention group (83% vs 93% completing the study)
Incomplete outcome data (attrition bias) HbA1c	Unclear risk	**Comment:** dropout rate was 7.6% at 4 weeks follow-up. All reasons for dropout were well described and valid. However, there seem to be higher dropouts in the intervention group (83% vs 93% completing the study)
Incomplete outcome data (attrition bias) Blood glucose	Unclear risk	**Comment:** dropout rate was 7.6% at 4 weeks follow-up. All reasons for dropout were well described and valid. However, there seem to be higher dropouts in the intervention group (83% vs 93% completing the study)
Selective reporting (reporting bias)	Unclear risk	**Comment:** no study protocol was available

Wan Seman 2016 *(Continued)*

Other bias	Low risk	**Comment**: none identified

Zaghlol 2021

Study characteristics	
Methods	**Study design**: open-label, parallel randomised controlled trial
Participants	**Inclusion criteria**: participants were adults (≥ 18 years) who expressed an intention to fast during Ramadan, adherent to one of the 4 hypoglycaemic regimens (metformin and glimepiride; metformin and vildagliptin; metformin and insulin glargine U100; metformin, insulin glargine U100 and human regular insulin) for at least the past 3 months **Exclusion criteria**: people with type 1 diabetes, latent autoimmune diabetes, secondary diabetes or autoimmune neuropathy, those who were pregnant or breastfeeding, previous history of diabetes ketoacidosis, hyperosmolar hyperglycaemia within the last 3 months, those who received niacin or corticosteroids within one month, HbA1c < 6.0% or exceeding 11.0%, history of recurrent hypoglycaemia, hypoglycaemia unawareness, those who had chronic impaired renal function (stage IV and V), liver cirrhosis, uncontrolled epilepsy, depressive disorder, bipolar disorder, psychotic disorder or cognitive dysfunction **Diagnostic criteria**: — **Setting**: tertiary care centre in Amman, Jordan **Age group**: adults aged ≥ 18 years old **Gender distribution**: 50:50 (females:males ratio) **Country where trial was performed**: Jordan
Interventions	**Intervention**: reduced dosage therapy **Comparators**: regular dosage therapy **Duration of intervention**: 29 days **Duration of follow-up**: — **Run-in period**: — **Number of trial centres**: —
Outcomes	**Reported outcome(s) in full text of publication**: hypoglycaemic events, incidence of diabetic ketoacidosis and hyperosmolar hyperglycaemic state
Study details	**Trial identifier**: NCT04237493. **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: — **Publication status**: full original article in a peer-reviewed journal
Stated aim for study	**Quote**: "We aimed to investigate the effect of dosage reduction of four hypoglycemic multidrug regimens on the incidences of acute glycemic complications in people with type 2 diabetes who fast during Ramadan."

Zaghlol 2021 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "We enrolled participants and randomly assigned them (2:1 ratio) to low- or regular-dosage therapy." **Comment:** insufficient information on how sequence generation was generated
Allocation concealment (selection bias)	Low risk	**Quote: "**A research assistant, who was otherwise not involved in the study, generated the allocation sequence and enclosed the assignments in sequentially numbered, opaque, sealed envelopes." **Comment:** independent team who had performed and conducted allocation concealment
Blinding of participants and personnel (performance bias) Hypoglycaemic episodes	High risk	**Quote:** "an open-label, parallel-group, randomized controlled trial at a tertiary care center in Amman, Jordan." **Comment:** this was an open-label trial with self-reported outcome of hypoglycaemic episodes
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemia	Unclear risk	**Quote:** "an open-label, parallel-group, randomized controlled trial at a tertiary care center in Amman, Jordan." **Comment:** this was an open-label trial with self-reported outcome of diabetic ketoacidosis or hyperosmolar hyperglycemic state
Blinding of outcome assessment (detection bias) Hypoglycaemic episodes	High risk	**Comment:** this was not clearly stated in the article but the outcome was reported by participants who were not blinded
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	**Comment:** this was not clearly stated in the article but the outcome was reported by participants who were not blinded
Incomplete outcome data (attrition bias) Hypoglycaemic episodes	Low risk	**Comment:** dropout rate was 1.3% at the end of study. All reasons for dropout were well described and valid.
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemia	Low risk	**Comment:** dropout rate was 1.3% at the end of study. All reasons for dropout were well described and valid.
Selective reporting (reporting bias)	Unclear risk	**Comment:** no study protocol was available or found
Other bias	Low risk	**Comment**: None identified

—: denotes not reported; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; DPP-4: dipeptidyl-peptidase 4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon like peptide-1; HbA1c: glycated haemoglobin; IV/IWRS: web/voice response system; MDRD: modification of diet in renal disease; NYHA: New York Heart Association; SGLT-2: sodium glucose co-transporter-2;

SMBG: self-monitoring of blood glucose; SMPG: self-monitoring of plasma glycose; SU: sulphonylurea; T2DM: type 2 diabetes mellitus; UNL: upper normal limit; WHO: World Health Organization
Note: where the judgement is 'Unclear' and the description is blank, the study did not report that particular outcome.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akram 1999	Study duration less than 30 days
Cesur 2007	Observational study
Glimiperide Study Group 2005	Observational study
Hajjaji 2019	Quasi-experimental study
Institut de Recherches International Servier 2007	Study withdrawn
IRCT201702269856N5	Examined healthy participants
Japar 2022	Quasi-experimental study
Khamseh 2013	Quasi-experimental study
Mattoo 2003	Study duration less than 30 days
McEwen 2015	Observational study
Mohamed 2019	Quasi-experimental study
NCT00664534	Not conducted during Ramadan period
NCT02694263	Authors responded that study was withdrawn prematurely and no study results available
Prataksitorn 2014	Quasi-experimental study
Shafras 2020	Quasi-experimental study
Susilparat 2014	Quasi-experimental study

Characteristics of studies awaiting classification *[ordered by study ID]*

Aghili 2012

Methods	**Type of trial:** efficacy trial **Allocation**: random **Intervention model**: parallel assignment **Masking**: — **Primary purpose**: treatment
Participants	**Condition**: type 2 diabetes

Aghili 2012 *(Continued)*

	Estimated number of participants: 40 **Inclusion criteria**: none stated **Exclusion criteria**: none stated
Interventions	**Intervention**: monitoring of blood glucose using a structured method (7 times daily, 3 days per week) **Comparator**: conventional blood glucose monitoring (4 times per week, 2 times before Iftar and 2 times after Iftar)
Outcomes	**Primary outcome**: — **Relevant proposed outcome measures for SoF table**: none
Study details	No publication data available
Publication details	**Publication type:** conference abstract **Language:** English
Stated aim of study	**Quote**: "to investigate whether this kind of fasting and its combination with structured self-monitoring of blood glucose (SMBG) can be beneficial in controlling blood glucose level and lipid profile of T2DM patients."
Notes	Contacted author for clarification

Mohamad 2018

Methods	**Type of trial:** non-inferiority trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: type 2 diabetes **Estimated number of participants:** 16 **Inclusion criteria**: none stated **Exclusion criteria**: none stated
Interventions	**Intervention**: dapagliflozin **Comparator**: liraglutide **Country**: Malaysia **Setting**: outpatient hospital
Outcomes	**Primary outcome**: compare the efficacy of liraglutide compared to dapagliflozin **Relevant proposed outcome measures for SoF table**: none

Mohamad 2018 *(Continued)*

Study details	No publication data available
Publication details	**Publication type:** conference abstract **Language:** English
Stated aim of study	**Quote**: "This study aimed to demonstrate efficacy of liraglutide compared to dapagliflozin in Ramadan"
Notes	

Yusoff 2017

Methods	**Type of trial:** non-inferiority trial **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: open-label **Primary purpose**: treatment
Participants	**Condition**: type 2 diabetes **Estimated number of participants:** 28 **Inclusion criteria**: none stated **Exclusion criteria**: none stated
Interventions	**Intervention**: dapagliflozin 10 mg once daily **Comparator**: saxagliptin 5 mg once a day **Country**: Malaysia **Setting**: outpatient hospital
Outcomes	**Primary outcome**: compare glycaemic variability of patients with type 2 diabetes on dapagliflozin and saxagliptin during Ramadan **Relevant proposed outcome measures for SoF table**: none
Study details	No publication data available
Publication details	**Publication type:** conference abstract **Language:** English
Stated aim of study	**Quote**: "To compare the glycaemic variability of Type 2 diabetic patients on Dapagliflozin and Saxagliptin during Ramadan fasting"
Notes	

ADDITIONAL TABLES

Table 1. Overview of trial populations

-Trial ID (trial design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Randomised (N)	Analysed (primary outcome) (N)	Finishing trial (N)	Randomised finishing trial (%)	Follow-up (extended follow-up)[a]
Al-Sifri 2011 (parallel RCT)	I: sitagliptin 100 mg once daily ± metformin	—	1243	529	507	513	97.0	—
	C: sulfonylurea (glimepiride, gliclazide or glibenclamide) ± metformin			537	514	521	97.0	
	total:			**1066**	**1021**	**1034**	**97.0**	
Anwar 2006 (parallel RCT)	I: repaglinide to a maximum of 4 mg 3 times a day	Sample size had 80% power to detect a difference in median blood glucose of 0.5	—	20	17	17	85.0	—
	C: glimepiride to a maximum dose of 6 mg daily			21	21	21	100	
	total:			**41**	**38**	**38**	**92.7**	
Aravind 2012 (parallel RCT)	I: sitagliptin 100 mg daily with or without metformin	—	1149	436	421	419	96.1	—
	C: sulphonylurea (glimepiride, gliclazide (immediate- or modified-release), or glibenclamide) with or without metformin			434	427	429	98.8	
	total:			**870**	**848**	**848**	**97.5**	
Azar 2016 (parallel RCT)	I: liraglutide up to 1.8 mg/d + metformin	Sample size had 90% power to detect a difference of 23.5 µmol in change in fructosamine level from start to end of Ramadan	562	172	171	146	84.9	1 week (34 weeks)
	C: sulphonylurea (gliclazide, glipizide or glyburide/glibenclamide or glimepiride) + metformin			171	169	147	86.0	
	total:			**343**	**340**	**293**	**85.4**	

Table 1. Overview of trial populations *(Continued)*

Belkhadir 1993 (parallel RCT)	I: full dose of glibenclamide	Sample size had power to detect a 55% difference in standard deviation of glycated haemoglobin from start to end of Ramadan	—	199	183	183	92.0	—
	C: reduced dose of glibenclamide (75% of normal dose)			198	182	182	91.9	
	total:			**397**	**365**	**365**	**91.9**	
Brady 2014 (parallel RCT)	I: liraglutide titrated to 1.2 mg/day	Sample size had 80% power to detect a difference of 22% in those achieving endpoint of HbA1c < 7%, no weight gain and no severe hypoglycaemia, assuming a dropout rate of 15%	—	47	32	32	68.1	—
	C: sulphonylurea (gliclazide, glimepiride and glibenclamide) either daily or twice daily depending on investigators preference			52	38	38	73.1	
	total:			**99**	**70**	**70**	**70.7**	
Hassanein 2014 (parallel RCT)	I: vildagliptin 50 mg twice daily + metformin at dosage between 1500 mg and 2500 mg daily	—	—	279	239	239	85.7	—
	C: gliclazide in multiples of 80 mg + metformin at dosage between 1500 mg and 2500 mg daily			278	239	239	86.0	
	total:			**557**	**478**	**478**	**85.8**	
Hassanein 2018 (parallel RCT)	I: insulin degludec/insulin aspart + oral antidiabetics	—	468	131	131	121	92.4	4 weeks (32 weeks)
	C: biphasic insulin aspart 30 + oral antidiabetics			132	132	127	96.2	
	total:			**263**	**263**	**248**	**94.3**	
Hassanein 2019	I: lixisenatide + basal insulin ± metformin	Sample size was calculated assuming 53% of people receiving SU and 15% receiv-	234	92	91	89	96.7	—

Table 1. Overview of trial populations *(Continued)*

(parallel RCT)	C: sulfonylurea + basal insulin ± metformin	ing lixisenatide had at least one documented symptomatic hypoglycaemia event during the Ramadan fast, assuming a 15% dropout rate		92	90	90	97.8	—
	total:			**184**	**181**	**179**	**97.3**	—
Lee 2015 (parallel RCT)	I: telemonitoring with goal-setting and feedback + Ramadan-focused diabetes education	—	128	18	18	14	77.8	—
	C: Ramadan-focused diabetes education			19	18	18	94.7	
	total:			**37**	**36**	**32**	**86.5**	
Lee 2017a (parallel cluster-RCT)	I: remote telemonitoring with feedback + Ramadan-focused diabetes education	Sample size was based upon an 80% power to detect a 25% difference in hypoglycaemia between two groups, assuming a 20% dropout rate	1034	45	45	31	68.9	—
	C: self-monitoring of glucose + Ramadan-focused diabetes education			40	40	34	85.0	
	total:			**85**	**85**	**65**	**76.5**	
Lum 2018 (parallel RCT)	I: collaborative empowerment programme	—	72	30	30	30	100	—
	C: usual care			32	32	32	100	
	total:			**62**	**62**	**62**	**100**	
Mafauzy 2002 (parallel RCT)	I: repaglinide	Sample size was based upon a 81% power to detect a difference of <25 µmol in change in fructosamine level	—	116	116	97	83.6	—
	C: glibenclamide			119	119	100	84.0	

Table 1. Overview of trial populations *(Continued)*

		from baseline between treatment group						
	total:			**235**	**235**	**197**	**83.8**	
Mahla 2014 (parallel RCT)	I: vildagliptin 50mg bd + metformin	—	—	30	—	—	—	—
	C: long-acting sulphonylurea medication regimen (glimepiride or gliclazide) with metformin			39	—	—	—	
	total:			**69**	**44**	**44**	**63.8**	
Shehadeh 2015 (parallel cluster-RCT)	I: levemir + NovoMix 70	Sample was based upon a non-inferiority margin of 27 mg/dL between both groups	317	127	127	124	97.6	—
	C: standard care			118	118	114	96.6	
	total:			**245**	**245**	**238**	**97.1**	
Wan Seman 2016 (parallel RCT)	I: dapagliflozin + metformin	—	325	65	58	54	83.1	—
	C: sulfonylurea + metformin			54	52	50	92.6	
	total:			**119**	**110**	**104**	**87.4**	
Zaghlol 2021 (parallel RCT)	I: dosage reduction of regular regimen	—	1026	458	452	452	98.7	—
	C: standard of care			229	226	226	98.7	
	total:			**687**	**678**	**678**	**98.7**	
Grand total	**All interventions**			2794		2561[b]		
	All comparators			2565		2368[b]		
	All interventions and comparators			5580		5181		

— denotes not reported

[a]Follow-up under randomised conditions until end of trial (= duration of intervention + follow-up post intervention or identical to duration of intervention); extended follow-up refers to follow-up of participants once the original trial was terminated as specified in the power calculation.

[b]Total does not include number of participants who completed study in the following studies: Mahla 2014.

C: comparator; **HbA1c**: glycosylated haemoglobin A1c; **I:** intervention; **RCT**: randomised controlled trial; **SU**: sulphonylurea.

HISTORY

Protocol first published: Issue 11, 2018

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

Shaun Wen Huey Lee (SWHL): protocol draft, acquisition of study reports, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Won Sun Chen (WSC): acquisition of study reports, study selection, data extraction and data analysis.

Renukha Sellappans (RS): study selection and data extraction.

Shakirah Binti Md Sharif (SBMS): protocol draft, study selection and data interpretation.

Maria-Inti Metzendor (MIM): drafted and conducted search; review of draft.

Nai Ming Lai (NML): protocol draft, data extraction, data analysis and future review updates.

DECLARATIONS OF INTEREST

Shaun Wen Huey Lee (SWHL): was the lead author of two of the included studies (Lee 2015; Lee 2017a). However, he was not involved in the selection and risk of bias assessment of these studies. He has no other known conflicts of interest.

Nai Ming Lai (NML): no known conflicts of interest.

Won Sun Chen (WSC): no known conflicts of interest.

Renukha Sellappans (RS): no known conflicts of interest.

Shakirah Binti Md Sharif (SBMS): no known conflicts of interest.

Maria-Inti Metzendor (MIM): no known conflicts of interest. MIM is an Information Specialist for Cochrane Metabolic and Endocrine Disorders, but she was excluded from the editorial processing of this article.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other

  No sources of support supplied

External sources

- No sources of support supplied, Other

  No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included additional outcomes in our review as these outcomes were also reported in the trials. These were the following:

- Serum fructosamine levels
- Fasting plasma glucose

The editorial base changed some of the wording and methods of our protocol according to the latest updates of the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards and the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021):

- The secondary outcome "socioeconomic effects" was deleted because it requires additional methods that were not planned for this review.

NOTES

We have based parts of the Methods on a standard template established by Cochrane Metabolic & Endocrine Disorders.