The safety and effectiveness of non-insulin glucose lowering agents in the treatment of people with Type 2 Diabetes who observe Ramadan: A systematic review and meta-analysis

Running title: Non-insulin glucose lowering agents in Ramadan

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Abstract

Aims: To determine which non-insulin glucose lowering treatment regimens are most appropriate in people with type 2 diabetes who choose to fast during Ramadan.

Materials and methods: Electronic databases were searched for randomised controlled trials (RCT) and observational studies comparing non-insulin glucose lowering agents in people with type 2 diabetes fasting during Ramadan reporting hypoglycaemia, weight and HbA1c change were included. Data were pooled using random effects models.

Results: Sixteen studies included; nine RCTs and seven observational studies. There was evidence that DPP-4 inhibitors led to less hypoglycaemic events compared to sulphonylureas. Sitagliptin significantly reduced the number of patients ≥1 hypoglycaemic episodes during Ramadan (RR 0.48, 95%CI 0.36, 0.64, p>0.0001), this was not replicated in the RCTs of vildagliptin but a significant reduction was found in the observational studies (RR 0.28, 95%CI 0.10, 0.75, p=0.01) with high heterogeneity (I^2=86.7%). Significant reductions in HbA1c and weight were seen in the observational studies of vildagliptin vs. sulfonylureas. The use of liraglutide led to significant weight loss (-1.81kg, 95%CI -2.91, -0.71, p=0.001) compared to sulfonylureas. Pioglitazone significantly increased weight compared to placebo (3.48kg, 95%CI 2.82, 4.14, p<0.0001).

Conclusions: The analysis supports the use of DPP-4 inhibitors during Ramadan over sulfonylureas for reduction in hypoglycaemic episodes without a cost to diabetes control and weight. The GLP-1 agonist liraglutide provides clinical benefits, but more studies are required. RCTs of DPP-4 inhibitors against GLP-1 agonists and novel therapies including

the SGLT-2 and alpha-glucosidase inhibitors are needed to inform evidence based guidelines.

Introduction

There are over 1.6 billion Muslims world-wide, constituting 23% of the total global population [1]. Ramadan is one of the five pillars of the Islamic faith and represents a significant cultural, religious and social identifier for many Muslims [2], the majority of Muslims participate in this holy month. Observance of Ramadan requires fasting from dawn to sunset, abstaining from eating and drinking during daylight hours, most Muslims will consume two meals each day [2]. The timing of Ramadan follows the lunar calendar, therefore the length of the fast varies depending on the time of year and the geographical location [2] but is usually between 10-20 hours.

The Quran exempts "sick" people from fasting, including pregnant, lactating or menstruating women, elderly and those suffering from chronic illness [2]. Concern for Muslims with diabetes during Ramadan has been recognised by religious leaders and an agreement was signed between the two leading bodies, the Islamic Organisation for Medical Sciences and the International Islamic Fiqh Academy [3] with the aim of aiding individuals to make informed decisions about fasting during Ramadan with support from their physicians [4]. However, many Muslims with diabetes do not consider themselves to be sick and are eager to fast. The EPIDIAR study identified that 43% of people with type 1 diabetes and 79% of people with type 2 diabetes (T2DM) fasted for at least 15 days during Ramadan [2]. Globally it is estimated that 50 million Muslims with T2DM fast during Ramadan [5]. However, the proportion of those with T2DM who observe Ramadan varies considerably between 58% to 90% amongst different Islamic countries [2].

The associated risks of fasting in those with diabetes include; hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, venous thromboembolisms and dehydration. The

EPIDAR study highlighted an increased risk of severe hypoglycaemia in people with T2DM fasting during Ramadan compared to other months of the year [2]. This can lead to discontinuation of medication and/or over compensating when fast is broken leading to hyperglycaemia [6]. A number of clinical guidelines for people with diabetes who chose to fast have been published [6-10], however, these recommendations are largely based on expert consensus and many health professionals feel poorly qualified to provide some of the recommendations. It is paramount that health professionals respect their patient's choice to fast whilst simultaneously employing their knowledge based on best evidence to provide them with the safest management and treatment options.

The aim of this systematic review and meta-analysis was to evaluate evidence on the safety and efficacy of non-Insulin glucose lowering regimes in those with T2DM observing Ramadan.

Materials and methods

A protocol was written prior to commencement of the systematic review and submitted to PROSPERO repository (http://www.crd.york.ac.uk/PROSPERO/).

Data sources and searches

Eligible studies were identified through searches of Medline, Embase and 'OpenGrey' online from 1946 to 8th April 2014. Additional studies were identified through selected academics who have expertise in this area of research.

Study selection

Eligible study designs included randomised clinical trials (RCTs), non-randomised clinical trials and observational studies including cohort, case-control and cross-sectional studies. Conference abstracts, meta-analysis, systematic reviews, editorials, expert opinions and case reports were excluded.

Patient groups included were adults with T2DM with an intention to fast during Ramadan, who were on a glucose lowering treatment other than insulin or diet and lifestyle only. Eligible glucose lowering therapies included; metformin, meglitinides, sulfonylureas, thiazolidinediones, GLP-1 receptor analogues (glucagon-like peptide), alpha glucosidase inhibitors, DPP-4 inhibitors (dipeptidyl peptidase-4) and SGLT2 inhibitors (sodium-glucose co-transport 2). Patient groups excluded were those with type 1 diabetes, those not intending to fast, those with pre-diabetes or impaired glucose tolerance and those not taking any of the glucose lowering therapies in question.

The primary outcome examined was number of participants having one or more hypoglycaemic episodes during Ramadan. Secondary outcomes were severe episodes of hypoglycaemia, total number of hypoglycaemic episodes, and weight and HbA1c change one month after the end of Ramadan i.e. an approximate 8 week follow-up. This time-point was chosen because it was the most often reported follow-up time in the existing literature. A hypoglycaemic episode was defined as patient reported symptoms of hypoglycaemia or measured blood glucose of less than 3.9mmol/L without symptoms. A severe hypoglycaemic episode is defined as requiring third party assistance. When multiple time points are reported the time point closest to one month post Ramadan was analysed for HbA1c and weight.

Data extraction and quality assessment

Two authors independently reviewed papers to assess whether they met the inclusion criteria. Of the papers included the data was extracted, in a standardised format by two authors with any discrepancies resolved by another.

We assessed the risk of bias of each study. We used the Cochrane Collaboration assessment for the RCTs [11]. Whilst there is no validated tool to assess risk of bias in observational studies, criteria have been published [12]. We used relevant questions from this checklist to assess consistent inclusion criteria, recruitment strategy, and follow up, high or differential lost to follow up, assessment of confounding, selective reporting and any other issues which may cause bias. Each area assessed for both types of study were graded as low risk, high risk or unclear.

Data Synthesis and Analysis

Each treatment comparison was analysed separately and analysis was performed by study type (observational and RCTs).

The risk ratio (RR) and 95% confidence intervals (CIs) were used to summarize the effect size for dichotomous outcomes (number of participants with at least one hypoglycaemic event as previously defined and number of participants with at least one severe hypoglycaemic event), and the rate ratio and 95% CIs were calculated for event rates (number of hypoglycaemic episodes per person year), these were also combined using a random effects model. Studies reporting no events in both arms were excluded, a 0.5 correction was applied to those reporting no events in a single arm [11]. For the analysis of rates, Ramadan was assumed to be 30 days in duration across all studies, regardless of actual days fasted by participants. The I^2 statistic was used to quantify the proportion of total variation that was due to statistical heterogeneity.

For the continuous outcomes (HbA1c and weight) mean change from baseline and standard deviation (SD) for each intervention group was extracted and the weighted mean differences in change from baseline from each study were synthesised using a random effects model. All studies collected baseline data ranging between 1 and 12 weeks prior to the commencement of Ramadan. The majority of the studies included did not report the SD for the change from baseline, therefore these were imputed using the baseline and follow up SDs and a correlation coefficient which was derived using individual participant data for the Treat 4 Ramadan study [11, 13]. Where SDs were not reported at follow up these were assumed to be equal to those reported at baseline [11]. Where the number of participants at follow up was not reported and could not be calculated this was assumed to be equal to the number randomised [11].

Meta regression including a variable denoting the study type (observational, RCT) was used to assess the difference in pooled treatment effect between study types.

Given the limited number of studies included, publication bias was not assessed. Stata (version 13) was used for all analysis. P<0.05 was considered statistically significant.

Results

Search

The search identified 496 results (Figure 1). Two additional papers were identified as suitable for inclusion by experts in the field [14, 15]. Full texts were then sought for 206 papers, of these ten additional duplicates were identified and three papers could not be obtained [16-18]. Sixteen papers were identified as fulfilling the inclusion criteria. All of the included papers were published in English.

Study Characteristics

The study characteristics are given in Table 1. Included studies were nine RCTs (2,927 participants) and seven observational studies (1,775 participants). All 16 reported hypoglycaemic events; 14 reported number of participants with one or more hypoglycaemic events, eight reported number of participants with one or more severe hypoglycaemic events and eight reported total number of hypoglycaemic events. Eleven studies reported change in HbA1c and nine studies reported weight change, for these outcomes the length of follow up was between 10-98 days post Ramadan (median 30 and 28 days for HbA1c and weight respectively). The majority of the studies compared vildagliptin with sulfonylureas (n=7), of which only two were RCTs. Two RCTs compared sitagliptin with sulfonylureas, and one RCT compared liraglutide to sulfonylureas. All of these studies included background metformin treatment in both arms. One RCT compared sitagliptin and metformin to sulfonylureas alone, four studies (two observational, two RCTs) compared repaglinide with sulfonylureas and one RCT compared pioglitazone to placebo. Of the RCTs six reported when treatment commenced prior to Ramadan, this varied from two weeks up to three months.

Risk of Bias Assessments

The results of the bias assessment for RCTs is given in Figure 2a. Overall there was poor reporting of the randomisation and allocation concealment, with only three of the nine RCTs reporting both of these in sufficient detail. The majority of studies were not blinded and used self-reported hypoglycaemia as the primary outcome, which could lead to bias. Only two RCTs were rated as having a low risk of bias across all of the items [14, 15].

The assessment of the observational studies is shown in Figure 2b. All of the observational studies included were prospective, following up groups based on their pre-Ramadan treatment regimen. Only one study adjusted for potential confounding [19].

Hypoglycaemia

In the observational studies, a significantly lower number of participants experienced one or more hypoglycaemic episodes when receiving vildagliptin compared to sulfonylurea during Ramadan (Table 2, Figure 3), this should be interpreted with caution given the high level of heterogeneity (I^2=86.7%). This was non-significant when pooling the two RCTs for the same treatments although overall no difference between the observational and RCT evidence was seen. No difference was seen between vildagliptin and sulfonylurea for severe events. A significantly lower number of participants experiencing one or more hypoglycaemic events was seen in the RCTs comparing sitagliptin to sulfonylureas with background metformin and when compared to sulfonylureas alone. This remained significant for the studies with background metformin treatment in both arms for severe events.

There were no significant differences between repaglinide or liraglutide versus sulfonylureas, and pioglitazone versus placebo for any of the hypoglycaemic outcomes, although there is limited data for all of these comparisons.

In terms of the number of hypoglycaemic episodes per person year, although fewer studies reported this outcome, similar results were found, with significantly reduced rates of hypoglycaemia in the observational studies comparing vildagliptin to sulfonylureas and in the RCT comparing sitagliptin to sulfonylureas.

HbA1c and weight Change

Table 2 shows the combined analysis in the 11 studies which reported change in HbA1c as an outcome one month post Ramadan. There was a significant decrease in HbA1c in the observational studies comparing vildagliptin with sulfonylureas, there was an increase in mean HbA1c in the RCTs with the same interventions, however this did not reach statistical significance. There was high heterogeneity in the observational studies (I^2=75.4%).   Although no effect was seen in the observational studies of repaglinide verses sulfonylurea, the RCT did show a significant increase in HbA1c in those taking repaglinide.

Change in weight one month post Ramadan was reported in nine studies. There was a significant reduction in weight in the participants treated with vildagliptin compared to sulfonylureas in the observational studies.   The RCT comparing liraglutide with sulfonylureas showed significantly more weight lost in the liraglutide group than those receiving sulfonylureas. In the RCT comparing pioglitazone with placebo there was significant weight gain in the pioglitazone group.

Discussion

This is the first systematic review assessing non-insulin glucose lowering therapies in people with T2DM observing Ramadan. Although this review included data from nine completed RCTs they were spread across a number of comparisons with a maximum of two RCTs included in any one analysis. These data were complimented by a number of observational studies, but given the potential for bias less weight should be placed on the results from these. Overall the current evidence base is limited with many opportunities for future research.

Overall the results for the hypoglycaemia outcomes were mixed with the majority of comparisons showing no effect. We do though report a significantly lower number of all and severe episodes of hypoglycaemia in participants treated with DPP-4 inhibitors (vildagliptin and sitagliptin) during Ramadan compared to those treated with sulfonylureas. This is not unexpected given the differing mechanisms of action of these drugs. Nevertheless sulfonylureas are still the most common second line therapy for T2DM in combination with metformin due to their efficacy, tolerability and low cost [20, 21]. However, the American Diabetes Association (ADA) recommends that they are used with caution during Ramadan due to their associated increased risk of hypoglycaemia [6]. More recently the avoidance of long-acting sulfonylurea's has been recommended [22]. DPP-4 inhibitors are associated with lower risk of hypoglycaemia which makes them a suitable treatment choice in patients who chose to fast.

We report a significant decrease in HbA1c one month post Ramadan with vildagliptin compared to sulfonylureas in the observational studies only, which might suggest that this reduction in hypoglycaemic episodes does not come at a cost to overall glucose control.

Furthermore, we report a greater reduction in weight with vildagliptin compared to sulfonylureas. Again this is an expected outcome given sulfonylureas are typically associated with a weight-gain of 1-4kg [23] and DPP-4 inhibitors are reportedly weight neutral [24]. However, this is outside of the context of prolonged fasting and indeed these results provide further evidence of the potential benefits of this therapy during Ramadan beyond improved glycaemic control. Importantly the two RCTs did not show statistical differences in HbA1c and weight with vildagliptin over sulfonylureas. It is important to note that none of the studies included in this systematic review collected data on diet and where physical activity was measured it was by self-report. This data is important given the potential for over-eating at the break of fast and the potential impact of this on glucose control. Future studies should consider collect data on changes in overall caloric intake, energy expenditure and diet composition.

Three RCTs have assessed sitagliptin against sulfonylureas. The meta-analysis of the two RCTs using background metformin in both arms showed significantly less hypoglycaemic episodes and severe hypoglycaemic episodes when compared to sulfonylureas during Ramadan. No trials have published data regarding change in HbA1c or weight for this comparison. Current NICE guidelines support the use of DPP-4 inhibitors if there is a risk of hypoglycaemia or if sulfonylureas are contraindicated or not tolerated [25]. Here we suggest that DPP-4 inhibitors may be at least as effective as sulfonylureas in terms of improved glycaemic control during prolonged fasting in addition to a reduced risk of hypoglycaemic events.

The studies comparing repaglinide with sulfonylureas are generally older (2002-2007) than those of DPP-4 and GLP-1 agonists (2009-2014). Repaglinide no longer forms part of the first line treatment for T2DM and therefore these results have been reported only for the

completeness of this review. Where pioglitazone was compared with placebo there was a significant increase in weight in the pioglitazone group, however the study authors attribute this mean 3 kg weight gain to oedema [14].

The Treat 4 Ramadan study was the first RCT to compare a GLP-1 receptor agonist, liraglutide, to sulfonylureas [13]. This study was positive on its primary outcome, a composite of HbA1c less than 7.0%, no weight gain and no severe hypoglycaemia and showed a significant weight reduction of -1.8 kg in this analysis. When assessing the number of participants experiencing one or more hypoglycaemic events during Ramadan, no difference was found between liraglutide and sulfonylureas. In contrast, when assessing the levels of hypoglycaemia over the duration of the trial the study reported a significantly lower incidence rate per person year in the liraglutide arm (IRR 0.58, 95% CI 0.39, 0.84, p=0.003) [13]. A significant HbA1c reduction was also seen in the liraglutide arm when adjusted for the stratification factors and baseline value [13]. Collectively these results support the potential use of a GLP-1 receptor agonist during Ramadan.

Implications for Practice

With a projected 55% increase in the total number of people with diabetes globally by 2035 the future burden of T2DM is set to increase [26]. The prevalence is projected to nearly double in the Middle East and North Africa and increase by 70% in South East Asia [26]. Three of the top ten countries for the prevalence of T2DM are in the Middle East (Kuwait 23%, Saudi Arabia 24% and Qatar 23%) [26]. With high numbers of Muslim patients with T2DM fasting in Ramadan in the Middle East evidence based clinical guidelines are needed. Whilst this study highlights areas where further research is needed, it also provides guidance for clinicians based upon the evidence available; that DPP-4 inhibitors are superior to sulfonylureas during Ramadan. This is with respect to hypoglycaemia and

weight and that GLP-1 receptor agonists also show clinical advantages as assessed by a composite endpoint [13]. As such clinicians should consider changing patients with T2DM not receiving insulin therapy who chose to fast during Ramadan from sulfonylureas to these therapies, we would recommend doing this prior to Ramadan so that a stable dose can be established before Ramadan commences. Clinicians should also counsel patients using evidence informed guidelines, with the overall benefit of reducing the risk of adverse events during Ramadan. The STEADFAST study highlights the benefits of combining DPP-4 inhibitors with non-drug interventions [15]. The study incorporated individualised Ramadan focused advice, with more contact between the patient and clinician than might otherwise occur [15]. Indeed focused education has been shown to decrease hypoglycaemic events in patients with T2DM on non-insulin treatment [27].

Implications for Research

The analysis highlights the need for more robust blinded large prospective RCTs looking at non-insulin glucose lowering agents during Ramadan. These studies need to be carried out in different geographical regions with different Muslim populations and preferably have subjects enrolled across a 12 month period which includes Ramadan. The latter would allow us to determine if the benefit of these medications is above that observed in patients outside the context of Ramadan.

No studies have compared GLP-1 agonists with DPP-4 inhibitors head to head during Ramadan. There have also been no trials examining other non-insulin glucose lowering agents such as SGLT2 inhibitors and alpha glucosidase inhibitors. Three SGLT-2 inhibitors have been approved for use in the European Union with more in development worldwide [28]. Dapagliflozin reduces fasting glucose with no more hypoglycaemia than placebo [28], Similarly, Canagliflozin is associated with reductions in high-density lipoprotein cholesterol and triglycerides, with low incidence of hypoglycaemia in those patients not receiving background SU therapy [29]. Most recently empagliflozin has been

reported to improve glycaemic control again without an increased the risk of hypoglycaemia [30] Given the likely increase in use and seemingly favourable side effect profiles, studies to examine these in patients fasting for Ramadan would be beneficial. Some clinicians may be apprehensive to recommend this class of drugs however, given SGLT2 inhibitors increase glucose urea and thus are associated with increased urination which may increase the risk of dehydration, particularly in the context of prolonged fasting. Thus this is a pertinent clinical question that requires answering. Acarbose, an alpha glucosidase inhibitor forms part of the NICE guidelines for T2DM but no studies have compared its use in Ramadan to other glucose lowering agents [25]. The single trial involving thiazolidinediones (pioglitazone) only compared with placebo. Trials to compare thiazolidinediones against other agents would be beneficial.

Strengths and Limitations

There are a number of limitations with the data available for this systematic review. In certain publications not all of the necessary statistical information was available on confidence intervals and standard deviations. Where this was the case information gained from similar studies was used in order that the study could be included in the analysis. In addition seven of the studies included are observational studies. The potential effects of external confounders that has not been adjusted for, which impacts on the results cannot be excluded. In the observational studies comparing DPP-4 inhibitors with sulfonylureas confounding is likely to have been a particular issue. DPP-4 inhibitors represent a newer drug class compared to sulfonylureas [25]. Patients on DPP-4 inhibitors may have been started on that medication because of worse glycaemic control or issues with weight gain or hypoglycaemia, this may bias the interpretation of the studies.

Unfortunately it was not possible to obtain full text for three publications identified in the initial literature search, although we think this is unlikely to have affected the results found. One paper written in German did not refer to a drug intervention in the title [16] and the

titles of the other two papers [17, 18] both suggested that they are not interventional studies.

Of the RCTs only two trials involved any sort of blinding [14, 15]. Patients and clinicians were aware of the treatment given in seven of the RCTs and this may have impacted on the results. Given that all studies reported hypoglycaemia episodes based partly or fully on self-reported patient symptoms the effect of bias in the way in which patients report symptoms cannot be excluded. Future studies may wish to consider using continuous glucose monitoring during Ramadan for an objective measure of hypoglycaemia.

Given these limitations in the data collected, the overall strength of the review is that it was possible to analyse all of the available published data as appropriate. Data from nearly 5,000 participants in 24 different countries were analysed to provide the basis of this meta-analysis.

Conclusion

Overall this systematic review and meta-analysis summarises the existing small evidence base. It suggests that DPP-4 inhibitors and possibly GLP-1 receptor agonists could be used during Ramadan over sulfonylureas for fewer hypoglycaemic episodes and a greater reduction in weight and possibly HbA1c. The results should be interpreted with caution however given the variable quality of the studies included. Clinicians can use this review to provide guidance based upon the evidence available for how to manage drug therapy in T2DM diabetes in Ramadan in those patients not taking insulin. There remains considerable need for further high quality research specifically in light of emerging new therapies.

Declaration of interests

M. J. D. has received funds for research, honorariums for speaking at meetings, and has served on advisory boards for Lilly, Sanofi Aventis, MSD, Novo Nordisk, BMS, BI and Roche. K. K. has received funds for research, honorariums for speaking at meetings, or served on advisory boards for Astra Zeneca, GSK, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk.

Contributor statements

LG, WH, MD, KK – conception; JD, LG, EB – conducted systematic review and drafted manuscript. LG – analysed data. WH, MD, KK - reviewed and edited the manuscript.

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Figure Legends

Figure 1. PRISMA Flow diagram

Figure 2. Risk of Bias Assessment – (a) Randomised Controlled Trials, (b) Observational Studies

Figure 3. Forest plot showing the risk of experiencing one or more hypoglycaemic events in those taking DDP-4 inhibitors versus sulphonylureas with background metformin treatment

Table 1. Characteristics of included studies

Author and Year	Interventions		% metformin	Treat Start (weeks)	Country	Outcomes Hypoglycaemia			HbA1c	Weight
						≥ 1 events	≥ 1 severe events	Total events		
Randomised Controlled Trials										
Abid 2013[31]	Sitagliptin + Metformin	Sulfonylurea	Only in Sitagliptin group	NR	Pakistan	Yes	No	No	No	No
Al-Sifri 2011[32]	Sitagliptin*	Sulfonylurea*	92	5	Egypt, Israel, Jordan, Lebanon, Saudi Arabia, United Arab Emirates	Yes	Yes	Yes	No	No
Anwar 2006[33]	Repaglinide	Sulfonylurea	0	12	Malaysia	No	No	Yes	No	No
Aravind 2012[34]	Sitagliptin*	Sulfonylurea*	84	NR	India, Malaysia	Yes	Yes	No	No	No
Brady 2014 [13]	Liraglutide*	Sulfonylurea*	100	2	United Kingdom	Yes	No**	No	Yes	Yes
Hassanein 2014 [15]	Vildagliptin*	Sulfonylurea*	100	8	Egypt, Lebanon, Tunisia, Russia, Indonesia, Germany, Jordan, Singapore, United Kingdom, Turkey, Spain, Malaysia, United Arab Emirates, Kuwait, Saudi Arabia, Denmark	Yes	No**	No	Yes	Yes
Mafauzy 2002 [35]	Repaglinide	Sulfonylurea	0	6	Malaysia, United Kingdom, France, Saudi Arabia, Morocco	Yes	No	Yes	Yes	No

Study	Intervention	Comparator	%		Country						
Malha 2014 [36]	Vildagliptin *	Sulfonylurea*	100	NR	Lebanon, USA	Yes	Yes	Yes	Yes	No
Vasan 2006 [14]	Pioglitazone	Placebo	0	10	India	No	Yes	Yes	No	Yes
Observational studies										
Al-Arouj 2013[37]	Vildagliptin*	Sulfonylurea*	89		Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, United Arab Emirates	Yes	Yes	No	Yes	Yes
Cesur 2007 [38]	Repaglinide	Sulfonylurea	0		Turkey	Yes	No	No	Yes	No
Devendra 2009 [19]	Vildagliptin *	Sulfonylurea*	100		United Kingdom	Yes	Yes	Yes	Yes	Yes
Halimi 2013 [39]	Vildagliptin*	Sulfonylurea* or Glinides*	100		France	Yes	Yes	No	Yes	Yes
Hassanein 2011 [40]	Vildagliptin*	Sulfonylurea*	100		United Kingdom	Yes	Yes	Yes	Yes	Yes
Shete 2013 [41]	Vildagliptin *	Sulfonylurea*	70		India	Yes	No	No	Yes	Yes
Sari 2004 [42]	Repaglinide	Sulfonylurea	0		Turkey	Yes	No	Yes	Yes	Yes

*Both arms included background Metformin treatment, ** zero events reported in both arms and therefore excluded from the analysis

Table 2. Hypoglycaemia during Ramadan and HbA1c and weight change post Ramadan

	No trials	RR[‡] (95% CI)	P value	I squared	Interaction[†]
Participants experiencing one or more hypoglycaemia episodes during Ramadan					
Vildagliptin vs. SU[*]					0.62
RCTs	2	0.73 (0.44, 1.23)	0.24	0%	
Observational studies	5	0.28 (0.10, 0.75)	0.01	86.7%	
Sitagliptin vs. SU[*]					-
RCTs	2	0.48 (0.36, 0.64)	<0.0001	0%	
Sitagliptin plus metformin vs. SU alone					-
RCT	1	0.40 (0.18, 0.87)	0.02	-	
Repaglinide vs. SU					0.81
RCT	1	0.91 (0.36, 2.28)	0.84	-	
Observational studies	2	0.55 (0.13, 2.42)	0.43	0%	
Liraglutide vs. SU[*]					-
RCT	1	0.68 (0.31, 1.50)	0.34	-	
Participants experiencing one or more severe hypoglycaemia episodes during Ramadan					
Vildagliptin vs. SU[*]					0.59
RCT	1	1.30 (0.09, 19.95)	0.85	-	
Observational studies	4	0.33 (0.09, 1.15)	0.08	0%	
Sitagliptin vs. SU[*]					-
RCTs	2	0.19 (0.04, 0.86)	0.03	0%	
Pioglitazone vs. placebo					-
RCT	1	0.21 (0.01, 4.14)	0.30	-	
All hypoglycaemic episodes per person-year during Ramadan					
Vildagliptin vs. SU[*]					0.17
RCT	1	0.95 (0.53, 1.72)	0.87	-	
Observational studies	2	0.06 (0.02, 0.23)	<0.0001	0%	
Sitagliptin vs. SU[*]					-

RCT	1	0.67 (0.53, 0.83)	<0.0001	-	
Repaglinide vs. SU					0.54
RCTs	2	0.70 (0.33, 1.50)	0.36	0%	
Observational study	1	0.16 (0.01, 3.94)	0.26	-	
Pioglitazone vs. placebo					-
RCT	1	1.16 (0.73, 1.86)	0.53	-	

	No trials	WMD (95% CI)	P value	I squared	Interaction†
HbA1c change post Ramadan					
Vildagliptin vs. SU*					0.11
RCTs	2	0.12 (-0.02, 0.26)	0.08	0%	
Observational studies	5	-0.23 (-0.41, -0.04)	0.02	75.4%	
Repaglinide vs. SU					0.41
RCT	1	0.38 (0.35, 0.41)	<0.0001	-	
Observational studies	2	0.14 (-0.21, 0.49)	0.44	0%	
Liraglutide vs. SU*					-
RCT	1	-0.27 (-0.61, 0.07)	0.12	-	
Weight change post Ramadan					
Vildagliptin vs. SU*					0.33
RCT	1	-0.20 (-0.75, 0.35)	0.48	-	
Observational studies	5	-0.65 (-0.96, -0.34)	<0.0001	41.6%	
Repaglinide vs. SU					-
Observational study	1	-0.40 (-1.36, 0.56)	0.41	-	
Liraglutide vs. SU*					-
RCT	1	-1.81 (-2.91, -0.71)	0.001	-	
Pioglitazone vs. placebo					-
RCT	1	3.48 (2.82, 4.14)	<0.0001	-	

*both group received background Metformin

† Test for the difference in effect between observational studies and RCTs

± Risk ratio shown for dichotomous outcomes, rate ratio for rate outcomes

Figure 1. PRISMA Flow diagram

Records identified through database searching Embase, Ovid and Open Grey (n=496)

Additional records identified through other sources (n =2)

Records after duplicates removed (n = 327)

Records screened (n = 327)

Records excluded (n = 121)

Full-text articles assessed for eligibility (n = 206)

Full-text articles excluded, with reasons (n =190)

Studies included in quantitative synthesis (meta-analysis) (n = 16)

RCTs (n=9)

Observational studies (n=7)

Further duplicates (n = 10)

Unable to obtain (n = 3)

Not RCT / Observational Study (n=142)

Not assessing non-insulins (n=28)

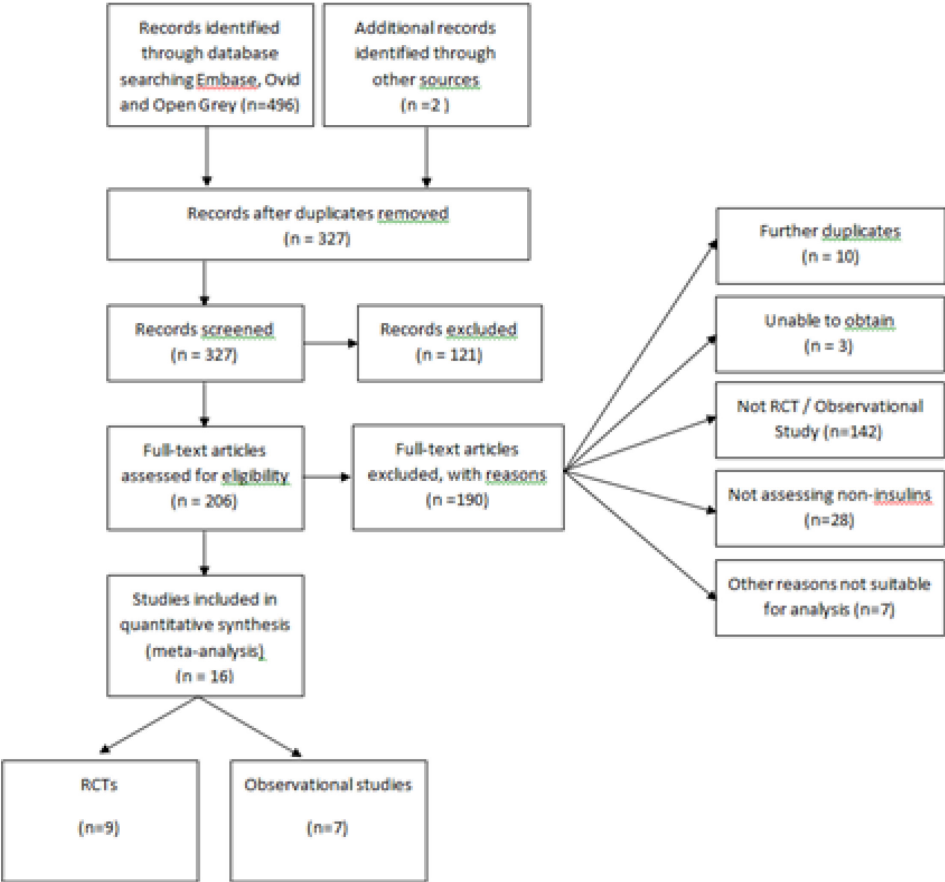Other reasons not suitable for analysis (n=7)

Figure 2. Risk of Bias Assessment – (a) Randomised Controlled Trials, (b) Observational Studies

(a)

	Random Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other
Abid 2013	?	?	?	?	+	-
Al-Sifri 2011	+	?	-	+	+	+
Anwar 2006	+	?	-	+	+	+
Aravind 2012	?	?	-	-	+	+
Brady 2014	+	+	-	+	+	+
Hassanein 2014	+	+	+	+	+	+
Mafauzy 2002	?	?	-	+	+	+
Malha 2014	?	?	-	-	+	+
Vasan 2006	+	+	+	+	+	+

(b)

	Consistent recruitment and inc/exc	Consistent length of follow up	High or differential lost to follow up	Selective reporting	Confounders taken into account	Other
Al-Arouj 2013	+	+	+	+	-	-
Cesur 2007	?	+	-	+	-	+
Devendra 2009	+	+	+	+	+	-
Halimi 2013	+	+	-	+	-	+
Hassanein 2011	+	+	+	+	-	+
Shete 2013	+	+	+	+	-	+
Sari 2004	+	?	?	+	-	+

Figure 3. Forest plot showing the risk of experiencing one or more hypoglycaemic events in those taking DDP-4 inhibitors versus sulphonylureas with background metformin treatment

Study ID		RR (95% CI)
Observational Studies: Vildagliptin vs. Sulphonylurea		
Devendra 2009		0.13 (0.03, 0.49)
Hassanein 2011		0.05 (0.00, 0.79)
Al-Arouj 2013		0.27 (0.19, 0.39)
Halimi 2013		0.92 (0.63, 1.34)
Shete 2013		0.15 (0.01, 3.12)
Subtotal (I-squared = 86.7%, p = 0.000)		0.28 (0.10, 0.75)
.		
RCTs: Vildagliptin vs. Sulphonylurea		
Hassanein 2014		0.71 (0.39, 1.28)
Malha 2014		0.81 (0.30, 2.23)
Subtotal (I-squared = 0.0%, p = 0.814)		0.73 (0.44, 1.23)
.		
RCTs: Sitagliptin vs. Sulphonylurea		
Al-Sifri 2011		0.47 (0.34, 0.67)
Aravind 2012		0.49 (0.29, 0.83)
Subtotal (I-squared = 0.0%, p = 0.891)		0.48 (0.36, 0.64)

NOTE: Weights are from random effects analysis

.00312   1   321

Favours DPP-4   Favours SU