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Comparative studies of dipeptidyl peptidase 4 inhibitor vs sulphonylurea among Muslim Type 2 diabetes patients who fast in the month of Ramadan: A systematic review and meta-analysis

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ABSTRACT

Aim: To systematically review the literature to compare the use of DPP4 inhibitors vs sulphonylurea in type 2 diabetic Muslim patients who fast in Ramadan, with regards to its safety, tolerability, glycemic control, and body weight changes.
Methods: All English-language medical literature published from inception till October 2014 which met the inclusion criteria were reviewed and analyzed.
Results: A total of nine papers were included, reviewed and analyzed. The total sample size was 4276 patients. All studies used either of the two DPP4 inhibitors – Vildagliptin or Sitagliptin, vs sulphonylurea or meglitinides. Patients receiving DPP4 inhibitors were less likely to develop symptomatic hypoglycemia (risk ratio 0.46; 95% CI, 0.30–0.70), confirmed hypoglycemia (risk ratio 0.36; 95% CI, 0.21–0.64) and severe hypoglycemia (risk ratio 0.22; 95% CI, 0.10–0.53) compared with patients on sulphonylureas. There was no statistically significant difference in HbA1C changes comparing Vildagliptin and sulphonylurea.
Conclusion: DPP4 inhibitor is a safer alternative to sulphonylurea in Muslim patients with type 2 diabetes mellitus who fast during the month of Ramadan as it is associated with lower risk of symptomatic, confirmed and severe hypoglycemia, with efficacy comparable to sulphonylurea.

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1. Introduction

During the Islamic month of Ramadan, Muslims are obliged to fast from dawn to dusk. During the fasting period, they abstain from all food and drinks. Although patients with illness are not required to fast, the EPIDIAR study, which involved 13 Islamic countries, showed up to 80% of patients with type 2 diabetes fast for at least 15 days during Ramadan [1,2].

Due to the abstinence in food and drinks, as well as the need to take anti hyperglycemic drugs, the rates of both hypoglycemia and hyperglycemia are increased during this period [3]. Despite that, it is interesting to note that the dose of anti-hyperglycemic medications, including both oral anti diabetic agent as well as insulin therapy, were maintained throughout the period of Ramadan in type 2 diabetes patients, recorded at 74.8% with the oral therapy and 64.1% among those using insulin therapy [2].

The use of sulphonylurea in patients with type 2 diabetes is one of the highest after Metformin [4]. However, this is associated with a higher risk of hypoglycemia, especially during the fasting period. An alternative to avoid hypoglycemia during Ramadan is to switch therapy to medications with lower risk of hypoglycemia.

Dipeptidyl peptidase 4 (DPP4) inhibitor is an incretin-based therapy which acts by inhibiting the DPP4 enzyme that rapidly metabolizes the gut hormone glucagon-like peptide-1 (GLP-1), leading to stimulation of insulin and inhibition of glucagon secretion. They are proven to be an effective oral agent in glycemic control [5–8], even as a monotherapy [9,10] which are associated with low risk of hypoglycemia [11,12].

The objective of this meta-analysis is to systematically review the literature and compare the use of DPP4 inhibitors vs sulphonylurea in type 2 diabetic Muslim patients who fast during Ramadan, with regards to its safety, tolerability, glycemic control, and body weight changes.

The primary outcomes are (1) the number of hypoglycemic events including symptomatic, documented and severe hypoglycemic events occurring during the fasting period and (2) the mean changes of HbA1C pre and post the month of Ramadan.

The secondary outcomes are (1) reported adverse events during the use of these medications, (2) body weight or body mass index changes pre and post Ramadan, and (3) proportion of patients who needed to break the fast while on these medications.

2. Methods

2.1. Data sources and extraction

We performed a systematic search of all English-language medical literature published from inception till October 2014 using PubMed, Embase and Ovid based on the following MESH headings “fasting”, “Ramadan”, “diabetes”, “Vildagliptin”, “Sitagliptin”, “Saxagliptin”, “Linagliptin”, “Anagliptin”, “Teneligliptin”, “Alogliptin”, and “Dipeptidyl peptidase 4 inhibitor”. We also looked into references of the selected papers. When papers were not available or information of the study cohort was inadequate, we made an attempt to contact the authors via email to obtain the full paper and more detailed data. The titles and abstracts obtained through the electronic search were screened followed by analysis of the full-text articles by two independent reviewers. All duplicates were removed. Wherever data was not provided numerically, it would be read off the graphs.

Data from eligible studies were extracted by one of the authors (HH), and all extracted data were reviewed by the second author (AY).

2.2. Study selection

Only studies which met the following criteria were included:

1. At least 10 patients with type 2 diabetes who fasted during the month of Ramadan.
2. Presence of control group using sulphonylurea.
3. Report of number of hypoglycemic events and number of patients who experienced hypoglycemic events during the period of Ramadan fasting.

2.3. Quality assessment

Each of the two reviewers independently assessed the quality of the methodology and reporting of the studies using Newcastle-Ottawa Scoring (NOS) Scale. Any discrepancies were sorted out by the third reviewer. The NOS scale was developed to assess the quality of non-randomized case control studies for interpretation of meta-analysis results. It uses a “star system” which judges the studies in three broad categories: the selection of study group, the comparability of the group, and the ascertainment of outcome of interest. It has a total score of 10.

2.4. Statistical analysis

2.4.1. Qualitative

All abstracted information was tabulated. A qualitative meta-analysis was conducted by summarizing, comparing and contrasting the abstracted data.

2.4.2. Quantitative

All the data analysis was done with Stats Direct (version 2.7.9). The presence of heterogeneity between the trials was tested using the I-squared (I^2) statistic. I^2 more than 40% indicated a significant heterogeneity. If the I^2 was significant, we pooled the data by using random effects (DerSimonian-Laird); if not, we pooled the data by using fixed effects (Mantel–Haenszel, Rothman–Boice). We also assessed publication bias with Begg–Mazumdar and Egger tests. For dichotomous data (symptomatic hypoglycemia, confirmed hypoglycemia and severe hypoglycemia), relative risks (RR) with 95% confidence intervals (CI) were estimated based on the random effects model. Continuous outcomes were analyzed with 95% confidence interval by using the effect size (weighted mean difference) meta-analysis if the mean and standard deviation of endpoint measures were presented in original articles. The adverse effects risk was calculated by proportional rate with 95% confidence interval.

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