

# Fasting during Ramadan: efficacy, safety, and patient acceptability of vildagliptin in diabetic patients

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**Abstract:** Diabetes management during Ramadan fasting is challenging to the physician in terms of minimizing the risk of hypoglycemia. As compared to oral hypoglycemic agents (OHAs) and sulfonylureas (SUs), which carry a higher and significant risk of hypoglycemia, newer antidiabetic agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors have demonstrated lower risk of hypoglycemia during Ramadan fasting, with better patient compliance. In addition to diabetes education and pre-Ramadan assessments, the physician should also consider use of DPP-4 inhibitors (such as vildagliptin) during Ramadan fasting to minimize the risk of hypoglycemia in type 2 diabetic subjects. Severe episodes of hypoglycemia have been demonstrated in recent research and clinical trials with OHAs/SUs. Conversely, these research observations have also demonstrated comparative safety and efficacy with lower risk of hypoglycemia associated with vildagliptin. Current research review has collected evidence-based clinical trials and observations for the drug vildagliptin to minimize the risk of hypoglycemia during Ramadan fasting, while at the same time focusing the role of diabetes self-management education (DSME), pre-Ramadan assessments, and patient care.

**Keywords:** hypoglycemia, DPP4-inhibitors, oral hypoglycemic agents, Ramadan fasting, type 2 diabetes, vildagliptin

## Introduction

It has been well documented in medical literature that diabetes management during Ramadan fasting poses challenges to the treating physician; and pre-Ramadan diabetes assessment, evaluations, and diabetes education are important for successful management.<sup>1</sup> This is because unplanned diabetes management during Ramadan fasting may lead to hypoglycemia. Hence, in the past few decades, efforts have been made by various researchers to manage diabetes during Ramadan fasting without the risk of hypoglycemia. Various strategies and therapies have been adopted in this regard during Ramadan fasting. These include alteration/reduction of the dosages for oral hypoglycemic agents (OHAs) and insulins, and shifting patients from OHAs and insulins to metformin or other agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors.

The increase in hypoglycemic events during the month of Ramadan has been previously reported in the literature. The Epidemiology of Diabetes and Ramadan (EPIDIAR) study has reported a 7.5-fold increase in risk of hypoglycemia in patients with type 2 diabetes.<sup>2</sup> However, this risk can be reduced by extensive diabetes education and pre-Ramadan medication adjustments.<sup>1</sup> Hence, Ramadan itself is not a risk, but poor education and use of medications which cause hypoglycemia with high dosages carries a risk.

Hypoglycemia itself has an adverse effect on the quality of life, is an obstacle while managing diabetes (to control glycemia), and is associated with poor compliance to

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medication and treatment. It has also been well documented that skipping meals and a reduced food intake are the main causes for the hypoglycemia during Ramadan fasting. Hence, diabetes education plays a central role, and diabetic patients should be given education and counseling before Ramadan fasting.<sup>1,3,4</sup> In general, severe hypoglycemia carries a risk of morbidities, with major cardiovascular events such as stroke, myocardial ischemia/failure, and ventricular arrhythmias.<sup>5</sup> For these reasons, allowing patients to fast/fasting during Ramadan without risk of hypoglycemia is a personal/patient-centered decision.

A study conducted in Saudi Arabia by Aziz<sup>1</sup> on 1,046 patients has demonstrated that Ramadan fasting itself does not pose a risk to human metabolism or health, but conversely has beneficial health effects on physiological parameters (eg, an opportunity to lose weight) and on chronic disease prevention. This study has demonstrated that this goal can be achieved only by optimal pre-Ramadan assessment and diabetes education.<sup>1</sup> Similar observations were reported in other studies as well.<sup>6–8</sup> However, in 2003, Laarijani et al<sup>9</sup> demonstrated a slight decrease in fasting serum glucose among healthy subjects during Ramadan fasting. A similar finding has also been demonstrated by Aziz<sup>1</sup> in the Ramadan study, with the lowest prevalence of hypoglycemia (4.58%). Contrary to these facts, different studies conducted in the past during Ramadan fasting have demonstrated high prevalence of hypoglycemia during Ramadan fasting (up to 21.7%).<sup>10–18</sup> However, these studies were mostly observational in nature, and patients were not selected before Ramadan for extensive diabetes self-management education (DSME), counseling, assessment for HbA1c/creatinine, and alteration of therapy. Hence in other words, it can be concluded, in general, that blood glucose levels fall during Ramadan fasting in diabetic and nondiabetic subjects, and prevention of hypoglycemia with medication adjustments/alterations are the basic strategies to manage diabetes during Ramadan fasting.

With this literature background, the current review focuses on a class of medications which does not cause hypoglycemia, both in general and during Ramadan fasting. One of them is DPP-4 inhibitors, and the drug available in the market is vildagliptin. We will focus on the pathophysiology of type 2 diabetes, DPP-4 inhibitors, and the role of vildagliptin during Ramadan fasting.

## **Pathophysiology of type 2 diabetes, DPP-4 inhibitors, and vildagliptin**

DPP-4 inhibitors are the new oral antidiabetic agents (including vildagliptin sitagliptin, saxagliptin, linagliptin, alogliptin

and other agents as well which are under extensive research). These agents/drugs reduce serum glucose concentrations and improve the glycemic control by augmenting the effects of “incretins”; hence this strategy is also called “incretin based therapy” for diabetes management.

Under normal physiological state, the gut, in response to meals, releases hormones called incretins, for example, GLP-1 (glucagon like peptide-1) and GIP (gastric inhibitory polypeptide), which augment biosynthesis and secretion of insulin (known as incretin effect) as well as slow gastric emptying as well.<sup>19–24</sup> Normally, these incretin hormones are degraded within minutes after their release by the enzyme DPP-4. As the DPP-4 inhibitors, inhibit this enzyme (DPP-4), they enhance or prolong incretin effect.

Contrary to this normal physiology, in diabetic patients the balance between insulin secretion and hepatic glucose production is dysregulated. In type 1 diabetic subjects, there is absolute insulin deficiency due to autoimmunity against  $\beta$ -cells with destruction of these cells, as compared with type 2 diabetic subjects who exhibit relative insulin deficiency with insulin resistance.<sup>25,26</sup> Furthermore, absolute or relative hyperglucagonemia, due to deficiency of incretin hormones in diabetic state, is a hallmark of both type 1 and type 2 diabetic subjects.<sup>27,28</sup> In other words, in type 2 diabetic subjects, there is insulin resistance and hyperglucagonemia. Due to these pathophysiological states, lipolysis and ketosis may worsen the metabolic state leading to diabetic ketoacidosis (DKA) during prolonged fasting, with absolute or relative insulin deficiency.<sup>29,30</sup> Insulin resistance can be reversed by metformin, and hyperglucagonemia by incretin based therapy. Additionally, vildagliptin has also been shown to improve  $\beta$ -cell function in type 2 diabetics, apart from enhancing incretin effect.<sup>31</sup> Other research studies have demonstrated efficacy of vildagliptin to lower HbA1c and improve glycemic control as well.<sup>32–36</sup> Hence, reversion of diminished incretin effect is also essential to manage diabetes effectively, both in general and during Ramadan fasting, while preventing hypoglycemia at the same time. This can be accomplished successfully by vildagliptin, a DPP-4 inhibitor. One of the interesting phenomena of DPP-4 inhibitor or vildagliptin is that it is blood glucose-dependent and does not cause hypoglycemia when given as monotherapy, which is again a therapeutic advantage of DPP-4 inhibitors/vildagliptin during Ramadan fasting.

## **Vildagliptin and Ramadan fasting**

In this section the literature for the safety and efficacy of vildagliptin during Ramadan fasting will be reviewed.

Sulfonylureas (SUs) and oral hypoglycemic agents (OHAs) are still widely used by general practitioners as oral antidiabetic agents, both in general and during Ramadan fasting, because of their ability to effectively reduce HbA1c and their low cost.<sup>37,38</sup> However, they carry a higher risk of severe hypoglycemia, especially if dose is not reduced during Ramadan fasting, and special precautions are required, together with individual considerations, especially in older age group.<sup>1,39</sup> Hence, highly variable rates of hypoglycemia have been reported in published research trials with SUs/OHAs (3%–40%) during Ramadan fasting. However, this risk was significantly reduced when vildagliptin was prescribed during Ramadan fasting, and this has also been recently reported in Indo-Pakistani populations from the UK and in cohorts of UK South Asian Muslim patients in the VECTOR (Vildagliptin Experience Compared To gliclazide Observed during Ramadan) study.<sup>40–42</sup> Furthermore, in general, these agents have also been demonstrated to be safer in older age group.<sup>43</sup>

A recent observational study which combined metformin and vildagliptin therapy together with or without OHAs during Ramadan fasting has demonstrated advantage of reduced hypoglycemia incidence.<sup>44</sup> They have shown one case of severe hypoglycemia in the arm treated with OHA compared to the vildagliptin group, which showed no hypoglycemia event. The hypoglycemia events were 12 times more in the group treated with OHA as compared to the vildagliptin group. Other studies have reported similar results when comparing OHAs with vildagliptin.<sup>45</sup> Another study conducted on vildagliptin and SUs or OHAs during Ramadan fasting has reported higher incidence of hypoglycemia during Ramadan fasting in the group treated with SU and Metformin vs vildagliptin plus metformin (26 episodes vs 19 episodes); and also reported HbA1c reduction in the vildagliptin group, however, with insignificant *P*-values.<sup>46</sup> A study conducted by Aziz<sup>1</sup> has also concluded that the patient group prescribed with DPP-4 inhibitors such as sitagliptin/vildagliptin did not show any episodes of hypoglycemia during Ramadan fasting. A recent review published in Switzerland and France has studied worldwide the role of DPP-4 inhibitors (including vildagliptin) during Ramadan fasting, and has come to the conclusion that the anti-diabetic agents DPP-4 inhibitors could be a more safer option while managing type-2 diabetes during Ramadan fasting, with a very low risk of hypoglycemia.<sup>47</sup>

Another prospective, noninterventional study published in France to assess real life rate of hypoglycemia during Ramadan fasting in patients with type 2 diabetes and their ongoing dual therapy of metformin–vildagliptin or metformin–sulfonylurea has shown that hypoglycemia as an

adverse events (AEs) was higher in SU group as compared to vildagliptin group (17.9% vs 7.5%; *P*=0.025), and better compliance was seen with vildagliptin group.<sup>48</sup>

The VIRTUE (Vildagliptin experience compared with sulphonylureas observed during Ramadan) study, which recruited 1,333 patients from 10 different countries worldwide, has demonstrated significantly fewer hypoglycemia events as compared with SU therapy (5.4% vs 19.8%, respectively; *P*<0.001). Additionally, good glycemic and weight control and better tolerance were observed in vildagliptin-treated patients.<sup>49</sup>

The STEADFAST (STudy Evaluating vildagliptin compared to gliclazide in patients with type 2 diabetes FASTing during Ramadan) study, a multicenter, double-blind, and randomized trial, which recruited 557 type 2 diabetic patients has demonstrated significantly lower hypoglycemia prevalence as compared to SUs (3.0% vs 7.0%, respectively; *P*=0.039).<sup>50</sup> Similar results have been reported in the Muslim populations of India.<sup>51</sup>

In summary, vildagliptin has been proven to be effective, well tolerated, and associated with low incidence of hypoglycemia in recent clinical trials. This is true especially in high risk population such as elderly and those with renal impairment or those who require insulin based therapy with metformin and DPP-4 inhibitors.<sup>44,52–56</sup>

## Conclusion

Despite the Islamic rule of exemption, most of the diabetic patients essentially fast during Ramadan; and this fact should be considered while managing diabetes during Ramadan fasting.<sup>1,2</sup> Drugs such as DPP-4 inhibitors/vildagliptin should be selected with other diabetes medications as these are not associated with high risk of hypoglycemia.

It has been observed that general practitioners have limited knowledge of diabetes management during Ramadan fasting. Furthermore, survey results have shown that 53% of patients fasted against medical advice.<sup>57</sup> However, this can be prevented effectively by extensive DSME and Ramadan-focused diabetes management; Ramadan Education and Awareness in Diabetes (READ) program and similar studies have demonstrated promising and good results in terms of minimizing hypoglycemia risk during Ramadan fasting.<sup>1,58,59</sup> Effective diabetes education for patients' empowerment and motivation with self-care awareness involves health care professional teams, families, the community, and religious authorities as well.<sup>60,61</sup>

Additionally, newer antidiabetic agents, such as vildagliptin (DPP-4 inhibitor), that are associated with lower risk of

hypoglycemia, are considered to be one of the safer options while managing diabetes during Ramadan fasting, and have also shown higher treatment adherence as compared to other medications.<sup>62</sup>

## Disclosure

The author reports no conflicts of interest in this work.

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