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ORIGINAL RESEARCH

Experience with Vildagliptin in Type 2 Diabetic Patients Fasting During Ramadan in France: Insights from the VERDI Study

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ABSTRACT

Aim: To assess in real life the rate of hypoglycemia during Ramadan in patients with type 2 diabetes (T2DM) in France, according to their ongoing dual therapy of metformin-vildagliptin or metformin-sulfonylurea/glinide (IS).

Methods: Prospective, non-interventional study with 2 visits (within 8 weeks before and 6 weeks after the end of Ramadan 2012). Study diaries were not used to collect events or record values of glucose monitoring. One hundred and ninety-eight patients on stable oral dual therapy for ≥2 months and with glycosylated hemoglobin (HbA_{1c}) ≤8.0% were recruited by 62 centers: 83 in the IS cohort and 115 in the vildagliptin cohort.

Results: Approximately 90% of patients were from Maghreb. The two cohorts were well balanced: 60% men, mean age 59 years, BMI 28 kg/m^2, metformin dose ~2,000 mg/day, and HbA_{1c} 7.2%. Distinct therapeutic management was planned in view of Ramadan with drug-

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adaptation intended in 61.4% of IS and 18.3% of vildagliptin patients. Hypoglycemia was reported in 37% of IS and 34% of vildagliptin patients; episodes declared as confirmed in 30.8% and 23.5%, respectively, and episodes documented as adverse event (AE) in 17.9% (22 episodes) and 7.5% (13 episodes), respectively ($P = 0.025$). Severe episodes were reported in 3.9% of IS and 1.7% of vildagliptin patients. 10.4% of IS and 2.6% of vildagliptin patients reported severe episodes and/or unscheduled medical visits due to hypoglycemia ($P = 0.029$). Glycemic control remained stable in both cohorts. Compliance with fasting was high, as well as adherence to drug with ≥5 missed-dose for 15.4% of IS and 8.5% of vildagliptin patients.

Conclusion: Although the overall frequency of malaise suggestive of hypoglycemia was high, which would be expected with prolonged fasting in a well-controlled T2DM population during hot summer days, the incidence of more severe and better-documented episodes (AE, severe event, event leading to unscheduled medical visit) were much lower, with consistently less events with vildagliptin therapy.

Keywords: Dipeptidyl peptidase-4 inhibitors; Hypoglycemia; Insulin secretagogues; Metformin; Ramadan; Type 2 diabetes; Vildagliptin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease with a worldwide prevalence that is rapidly increasing. In 2012, more than 371 million people were estimated to have T2DM [1]. As a result of urbanization and socioeconomic developments, the prevalence of diabetes has been rising by 10% annually in countries with large Muslim populations [2]. Almost a quarter (~1.6 billion) of the world's population follows Islam [3, 4]. Although a majority of them are spread across the Middle East, North Africa, and parts of Asia, there are about 4 million Muslims in France [5].

Ramadan is the ninth month of the Islamic lunar calendar, when healthy Muslims are obliged to abstain from food and drinks from sunrise to sunset [6]. Although the Koran [7] and several guidelines [4, 8, 9] exempt the sick from fasting, over 50 million Muslims with diabetes fast during the holy month of Ramadan each year worldwide [3, 10]. Epidemiologic data from the first large retrospective study (*EPI*demiology of *DIA*betes and *R*amadan [EPIDIAR]) conducted in 13 Islamic countries reported that a vast majority of patients with T2DM (79%) fasted for at least 15 days during Ramadan [11]. The dates of observance of Ramadan differ each year and the period of fasting also varies by geographical location and season, lasting up to 18 h or more during the summer months in the northern latitudes [4]. A majority of Muslim patients with diabetes are ardent about their Ramadan fasting, despite the potential complications of fasting, which may include hyperglycemia, hypoglycemia, and increased risk of dehydration and thrombosis [10, 12]. Prolonged fasting in the absence of adequate insulin may lead to excessive glycogen breakdown and increased gluconeogenesis, eventually leading to hyperglycemia [4, 10]. On the other hand, the risk of hypoglycemia is an important factor to be considered when choosing an antidiabetic agent [10]. This is of particular concern in the coming decade, as Ramadan will fall during the summer months, increasing the number of fasting hours and

eventually raising the risk of negative effects in patients with diabetes who wish to fast.

Hypoglycemia is one of the main health risks during this fasting period [12]. In the EPIDIAR study, there was a 7.5-fold increase in risk of severe hypoglycemia leading to hospitalization during the month of Ramadan as compared with other months (from 0.4 to 3 events/100 patients/month) in patients with T2DM [11]. The various recommendations for patients with diabetes who wish to fast include pre-Ramadan assessments, Ramadan-focused structured education, and regular blood glucose monitoring [4, 8, 9, 12, 13].

Sulphonylureas (SUs) and glinides are still widely used as oral antidiabetic agents during Ramadan because of their well-established clinical profiles and low cost [14, 15], but they are associated with an increased risk of hypoglycemia, and their use should be individualized with caution [4]. Highly variable rates of hypoglycemia have been reported in published studies with SUs and glinides [16], ranging from 3% in the *GLI*mepiride in *RA*madan (GLIRA) study [17] and about 40% in the *V*ildagliptin *E*xperience *C*ompared *T*o gliclazide *O*bserved during *R*amadan (VECTOR) study [18]. A recent five-country, observational study that included approximately 1,400 patients treated with SUs during Ramadan reported that the overall incidence of symptomatic hypoglycemic events was approximately 20% and the overall incidence of severe hypoglycemic events was 6.7%, with differences noted across countries and SUs (glipizide 28%, glibenclamide 26%, glimepiride 17%, and gliclazide 14%) [19].

Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has been shown to be effective and well tolerated with a low incidence of hypoglycemia in clinical trials up to 2 years across disease stages [20], including in higher-risk populations with more severe consequences of hypoglycemia, such as in elderly patients aged ≥75 years [21], patients with renal impairment [22], and insulin-treated patients [23]. The risk of severe hypoglycemia has been shown to be significantly reduced with vildagliptin versus SUs [24, 25]. The use of vildagliptin during Ramadan has also been recently reported, essentially in Indo-Pakistani populations from the UK [26] and in cohorts of UK South Asian Muslim patients (VECTOR study) [18]. However, little data exist on populations practicing Ramadan fasting in France. One such study recently conducted in Marseille, a crossover point between France and North Africa with a diverse religious population, showed the importance of Ramadan fasting for French Muslim patients and revealed a wide gap between the patients' and physicians' attitudes, highlighting the need for increased awareness and more medical training [27].

The present observational study, *V*ilagliptin *E*xperience during *R*amadan in patients with *DI*abetes (VERDI), aimed to evaluate the management of T2DM in France during Ramadan 2012 and the rate of hypoglycemia in patients receiving an ongoing dual therapy of metformin and vildagliptin or metformin and SU or glinide. Real-life educational approaches at the pre-Ramadan visit were collected, such as adaptation of drug treatment, blood glucose monitoring, and dietary counseling.

MATERIALS AND METHODS

Study Design

This was a multicenter, prospective, observational study conducted at 62 centers in France. General practitioners (GPs) and diabetologists with experience in managing T2DM patients wishing to fast during

Ramadan were invited to take part in the study: 1,649 physicians were contacted, 112 accepted, and 62 (56 GPs and 6 diabetologists) were active in recruiting patients between May 18, 2012 and July 18, 2012. Physicians were asked to include patients attending a routine consultation within ~8 weeks before the start of Ramadan. Based on the ongoing dual therapy with either metformin and vildagliptin (hereafter referred to as the vildagliptin cohort) or metformin and an insulin secretagogue (IS) (SU or glinide) (hereafter referred to as the insulin secretagogue [IS] cohort), the study population was divided into two cohorts. The choice of treatments was independent from the study participation and all treatments were used in accordance with the drugs' prescribing information. The Common International Names were not collected for the drugs in the IS cohort. The study was designed to have 2 visits: the first, or baseline, visit (Visit 1) within 8 weeks before the start of Ramadan (July 19, 2012) and the follow-up, or final, visit (Visit 2) within 6 weeks after the end of Ramadan (August 20, 2012). Prior to Ramadan, patients could receive specific dietary advice, and a glucometer could be prescribed for self-monitoring of blood glucose (SMBG), according to local practice. Because the study design was non-interventional, patients received follow-up as per usual clinical practice without protocol-mandated intervention. In particular, study diaries were not requested to record events or SMBG values. Prior to Ramadan, physicians could adjust the treatment (dose change and/or frequency of dosing) within each cohort to optimally manage their patients.

Patients

Patients included in the study met the following criteria: ≥18 years of age, with T2DM diagnosed at least 12 months prior to the start of Ramadan and who planned to fast at least 10 days during Ramadan; receiving dual therapy of either metformin and an IS (SU or glinide) or metformin and vildagliptin for at least 8 weeks before fasting begins, and at least 1 consultation scheduled within 6 weeks after Ramadan ends; a glycosylated hemoglobin (HbA_{1c}) level ≤8.0% approximately 1 month before the start of Ramadan; and no plans to spend Ramadan outside of France. Patients with a history of type 1 diabetes or a secondary form of diabetes, those requiring ≥3 oral antidiabetic therapies or insulin at study entry, and women who were either pregnant or breast-feeding were excluded from the study.

Study Assessments

The primary assessment was to evaluate the incidence of all hypoglycemic episodes during Ramadan in each of the 2 treatment cohorts. Hypoglycemic episodes were categorized as symptomatic; confirmed by self-monitoring using a glucometer (defined as ≤70 mg/dL); severe (defined by the need of a third party); reported as an adverse events (AE); and requiring an unscheduled medical visit. Secondary assessments included the percentage of patients in each group for whom therapeutic adaptations were planned prior to Ramadan and for whom treatment adaptations were actually made during Ramadan; percentage of patients in each group in whom the fast was interrupted; treatment adherence (number of missed doses and the proportion of patients who missed ≥5 doses); and changes from Visit 1 to Visit 2 in mean HbA_{1c} levels (with both measurements performed at the same local laboratory using the Diabetes Control and Complications Trial reference method) and body weight. All AEs and serious

AEs (SAEs) together with their severity and relationship to the study treatment were analyzed.

Statistical Analysis

Quantitative or continuous variables were described by mean and standard deviation (SD) and in some cases by median and range. Qualitative variables were described by absolute frequency and percentage per modality. Quantitative variables were compared between groups by student tests in case of normal distribution and Wilcoxon-Mann–Whitney test otherwise. Qualitative variables were compared between groups using the Pearson Chi-squared test if all theoretical sample sizes were ≥ 5 or using the Fisher test if <5. All tests were adjusted with a significance level of 5%. If demonstrated, a statistically significant association between treatment and hypoglycemic events would not allow concluding that the treatment is an independent predictive factor for hypoglycemic occurrence, since no adjustment for potential confounding factors was performed. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA). Sample size was set to guarantee sufficient accuracy of the rate of patients with hypoglycemic events, which is the main end point of the study.

Ethics

This observational study was conducted in accordance with the French Privacy Law and respecting the Recommendations for professional standards and good epidemiological practices (ADELF, EPITER, ADEREST, AEEMA 2007). Candidates for inclusion were provided with full information about the study in writing. All data processing was carried out in compliance with the French Information Technology and Privacy Law.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 218 patients ($n = 115$ for vildagliptin and $n = 83$ for IS) were included in the study. Before the start of the Ramadan fast, 5 patients from the IS cohort were switched to the vildagliptin cohort by their physician. All patients completed the study and 198 were kept in the final analysis: 120 patients in the vildagliptin cohort and 78 in the IS cohort. The remaining 20 patients were excluded from the study during the follow-up mostly due to missing or incomplete data and dual therapy unknown or modified during Ramadan. Patients were predominantly recruited by GPs (96%). Over one-third of these active physicians were practicing across the South of France, predominantly in Marseille.

The 2 cohorts were well balanced at baseline (Table 1). About 60% of patients were men; the mean age was 59.0 years with a mean diabetes duration of 7.4 years. Mean body mass index (BMI) was 28.1 kg/m^2 with a significant proportion of obese patients, especially women (40% of the women and 22% of the men had a BMI > 30 kg/m^2). Mean HbA_{1c} level was 7.2% in both cohorts with 28.7% of patients having an HbA_{1c} level >7.5%. Approximately 25% of patients had diabetes-related complications and 84% had at least 1 associated cardiovascular risk factor. In line with their cardiovascular risk profiles, two-thirds of the patients received concomitant therapies (half antihypertensive agents, half lipid-lowering, and approximately one-third antiplatelet agents). The duration of the dual antidiabetic

Table 1 Patient demographic and baseline characteristics

	Metformin + IS ***n* = 83**	**Metformin + vildagliptin** ***n* = 115**	**Total** ***N* = 198**
Age, years (SD)	59.8 (10.3)	58.4 (11.5)	59.0 (11.0)
Age group, years, %			
<50	18.1	20.9	19.7
50–<65	48.2	47.0	47.5
65–<75	25.3	26.1	25.8
≥75	8.4	6.1	7.1
Gender, male, %	55.4	63.5	60.1
Body weight, kg (SD)	78.4 (12.5)	79.3 (12.4)	78.9 (12.5)
BMI, kg/m^2	28.1 (4.8)	28.1 (4.0)	28.1 (4.3)
Men (BMI ≥ 30 kg/m^2), %	19.6	23.3	21.8
Women (BMI ≥ 30 kg/m^2), %	40.5	40.5	40.5
Region of origin, Maghreb, %	85.5	93.9	90.4
Duration of diabetes, years (SD)	8.1 (6.0)	6.9 (4.4)	7.4 (5.2)
HbA_{1c}, % (SD)	7.2 (0.6)	7.2 (0.6)	7.2 (0.6)
Frequency of daily drug intake, %			
Once a day	0.0	0.9*	–
Twice a day	33.7	69.3	–
Thrice a day	66.3	29.8	–
Treatment duration, years (SD)	3.5 (3.9)	1.1 (0.8)*	–
Metformin, mg			
Mean daily dose	2,155 (685)	2,190 (559)	–
Median, range	2,100 (850–3,000)	2,000 (700–3,000)	–
Diabetes complications, %	22.9	27.0	–
At least 1 microvascular complication	12.0	19.1	–
At least 1 macrovascular complication	18.1	16.5	–

Values are mean (SD) unless indicated otherwise
BMI body mass index, *HbA_{1c}* glycosylated hemoglobin, *IS* insulin secretagogue, *SD* standard deviation
* $P < 0.001$

therapy was longer in the IS cohort (3.5 years) than in the vildagliptin cohort (1.1 year) but the median total daily dose of metformin was identical in both (~2,000 mg/day). A majority of patients in the IS cohort received treatment 3 times a day (66.3%) versus only 29.8% in the vildagliptin cohort (i.e., additional metformin at noon). A vast majority of the patients (90.4%) originated from the Maghreb region (Algeria ~47%, Morocco ~28%, and Tunisia ~16%).

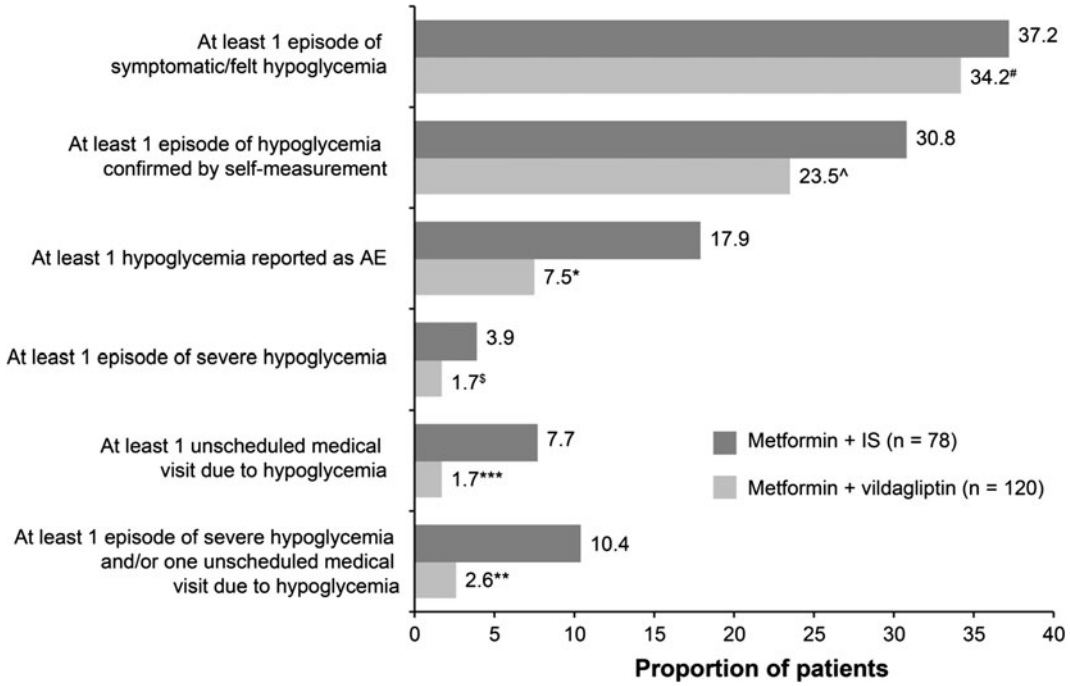

Fig. 1 Hypoglycemic events as declared by physicians. *AE* adverse event, *IS* insulin secretagogue. $^{*}P = 0.025$, $^{**}P = 0.029$, $^{***}P = 0.059$, $^{\wedge}P = 0.260$, $^{\$}P = 0.392$, $^{\#}P = 0.665$. An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Severe hypoglycemia means patient unable to initiate self-treatment and requires assistance of another person or hospitalization. Any unscheduled visit to a site during the observation period by patient due to hypoglycemia was considered as unscheduled medical visit related to hypoglycemia

Hypoglycemia

Data on all hypoglycemic episodes during Ramadan, as collected and reported a posteriori by physicians at the post-Ramadan visit, are presented in Fig. 1. In all categories of events, rates of hypoglycemia were numerically lower in the vildagliptin cohort as compared with the IS cohort. At least 1 episode of symptomatic hypoglycemia was reported during Ramadan in 37.2% of patients in the IS cohort and 34.2% of patients in the vildagliptin cohort ($P = 0.665$). The proportion of patients in whom at least 1 episode was declared confirmed by self-testing was 30.8% in the IS cohort and 23.5% in the vildagliptin cohort ($P = 0.260$). More hypoglycemic episodes were documented by physicians as AEs in the IS cohort (22 hypoglycemic events reported by 17.9% of patients), compared with the vildagliptin cohort (13 hypoglycemic events reported by 7.5% of patients) ($P = 0.025$). The proportion of patients reporting at least 1 severe episode of hypoglycemia that required third-party assistance was 3.9% in the IS cohort and 1.7% in the vildagliptin cohort ($P = 0.392$). In total, 7.7% of patients in the IS cohort resorted to at least one unscheduled medical visit during Ramadan because of hypoglycemia as compared with 1.7% in the vildagliptin cohort ($P = 0.059$). Overall, the percentage of patients with severe hypoglycemia and/or an unscheduled medical visit due to hypoglycemia was higher in the IS cohort than in the vildagliptin cohort (10.4% and 2.6%, respectively, $P = 0.029$).

Table 2 Therapeutic management of patients during Ramadan fast

	Metformin + IS $n = 78$	Metformin + vildagliptin $n = 120$
Treatment modification		
Treatment change, yes, %	66.7*	28.3
Type of treatment change, %		
No change	33.3	71.7*
Only metformin change	10.3	11.7
Only associated treatment change	15.4	2.5
Metformin and associated treatment change	41.0	14.2
Treatment adherence		
Number of times treatment not taken, %		
0	56.4	50.8
1–<5	28.2	40.7
≥5	15.4	8.5
Number of times treatment not taken due to hypoglycemia or fear of hypoglycemia, %		
0	69.2	69.7
1–<5	21.8	27.7
≥5	9.0	2.5
Patients who interrupted fasting ≥1 day, %	25.6	21.7

IS insulin secretagogue
* $P < 0.001$

Therapeutic Management

Overall, 95.5% of patients had previously observed Ramadan fasting while being diagnosed with T2DM. In terms of therapeutic management, dietary advice at the pre-Ramadan visit was provided to a similar number of patients in both cohorts (~85%). However, a treatment adaptation, with dose or frequency adjustment of the treatment, was planned prior to Ramadan more frequently in the IS cohort (61.4%) than in the vildagliptin cohort (18.3%, $P < 0.001$). About three-fourths of the patients, 80.5% in the IS cohort and 68.4% in the vildagliptin cohort ($P = 0.059$), were advised to self-monitor their blood glucose levels during Ramadan.

Treatment was actually modified for 66.7% of IS patients and 28.3% of vildagliptin patients during Ramadan ($P < 0.001$) (Table 2). Among patients for whom treatment was modified, a modification of metformin alone was made in 15.4% of patients in the IS and 41.2% of patients in the vildagliptin cohort, consisting mostly of dose reduction with suppression of the mid-day dose. The change predominantly involved the associated treatment in the IS cohort (85%) and consisted mostly of a dose reduction (in 68% of cases) with a change in timing (suppression of the mid-day dose in 34%

of the cases) and moving the morning dose to the evening (in 32% of cases).

Adherence to Treatment and Fasting

Overall, approximately 53% of patients adhered to their treatment during fasting without interruption. The proportion of patients who had missed ≥5 doses was lower in the vildagliptin cohort (8.5%) than in the IS (15.4%) cohort, including patients who missed ≥5 doses due to hypoglycemia or fear of hypoglycemia (2.5% and 9.0%, in the vildagliptin and IS cohorts, respectively) (Table 2).

Overall, patients fasted on an average for 29.8 days (range 16–31 days). A majority of patients completed fasting with minimal interruptions. Temporary diabetes-related interruptions of the fast for ≥1 day (mean of 3 days) were reported by 25.6% patients in the IS group and 21.7% patients in the vildagliptin group.

Glycemic and Weight Control

Glycemic control remained stable and similar in both cohorts (from a mean of 7.2% at Visit 1, mean HbA_{1c} level was 7.2% at Visit 2; 27.7% of patients had an HbA_{1c} level >7.5%). Body weight also remained stable in both cohorts (overall mean at Visit 2 of 78.3 kg: 77.9 kg in the IS cohort from a mean of 78.4 kg at Visit 1 and 78.6 kg in the vildagliptin cohort from a mean of 79.3 kg at Visit 1).

Adverse Events

Among the 198 patients, 24 patients had at least 1 AE; a total of 39 AEs were reported. One or more AEs were reported by 19.2% of patients in the IS cohort (25 AEs) and 7.5% of patients in the vildagliptin cohort (14 AEs). The difference was largely due to the incidence of hypoglycemia, which was reported as the most common AE (22 and 13 in the IS and vildagliptin cohorts, respectively) and were pre-specified as AEs of clinical relevance in the study. AEs suspected to be treatment-related were reported by 10.3% of patients in the IS cohort and 5.8% in the vildagliptin cohort. No event led to discontinuation and none were reported as an SAE. Other AEs, only reported in the IS cohort, were malaise, dizziness, and hyperhidrosis, all of which could be related to hypoglycemic episodes.

DISCUSSION

Despite the Islamic rule of exemption, many Muslim patients with diabetes choose to fast during Ramadan [11]. Additionally, fasting has been associated with a feeling of improvement in overall well-being, having a positive impact on social, cultural, and religious domains [28]. Health care professionals are seldom included in the spiritual decision as to whether or not a patient chooses to fast during Ramadan [27, 28]. The recent study by Gaborit and colleagues in France showed that many GPs had limited medical knowledge of Ramadan fasting in patients with diabetes, leading to over half of them proscribing fasting, even when it was not medically justified. On the other hand, 53% of patients fasted against medical advice. This wide gap between GPs' and patients' attitudes highlights the lack of training and subsequent difficulties in such cross-cultural patient-physician relationships [27]. However, structured educational programs, such as the Ramadan Education and Awareness in Diabetes (READ) program, have clearly shown positive effects [28], in particular in minimizing the risk of hypoglycemia [29, 30]. This Ramadan-focused diabetes education needs to involve not just the health care team but also the patients' families, friends, community, and

religious authorities. It empowers patients to adapt their lifestyle and also helps them take responsibility for their care beyond the Ramadan fast [29, 31, 32]. In addition to these educational programs, newer pharmacologic agents with a reduced risk of hypoglycemia, such as DDP-4 inhibitors, may be a safer option for patients with diabetes during fasting [4, 11].

In view of that consideration, the current prospective, real-life study primarily aimed to compare the incidences of hypoglycemia during Ramadan fasting between patients with T2DM treated with stable dual oral therapy of metformin and vildagliptin or metformin and IS. This observational study is one of the first to evaluate the therapeutic management of Ramadan fasting in French Muslim patients with well-controlled T2DM. It showed that all categories of hypoglycemic events were numerically lower in the vildagliptin cohort compared with the IS cohort. Overall, the frequency of malaise suggestive of hypoglycemia was relatively high in both cohorts, reported in about one-third of patients with a small between-group difference. This could be attributed to the prolonged fasting hours of over 18 h a day during hot summer days, making it difficult to ascertain the hypoglycemic nature of all malaise events. However, the overall frequency of better-documented hypoglycemic episodes and/or more severe events (hypoglycemic events reported as AEs, hypoglycemia requiring unscheduled medical visit, and severe episodes requiring third-party assistance) was lower in both cohorts, with consistently fewer events with vildagliptin therapy compared with traditional insulin secretors (SU or glinide). This finding is in line with recent observations and experience with vildagliptin during Ramadan in other populations and regions of the world. In a UK retrospective audit conducted in North West London with Muslim patients of mostly Pakistani and Middle Eastern origins, confirmed hypoglycemic events (defined as blood glucose <3.5 mmol/L with or without symptoms) were recorded during Ramadan in 2 (7.7%) patients receiving vildagliptin and 16 (61.5%) patients receiving gliclazide [25]. Similarly, in a UK observational study of South Asian patients, VECTOR, none of the 23 patients treated with vildagliptin as add-on to metformin reported hypoglycemia during Ramadan, in contrast to the 15 (41.7%) patients receiving SU therapy [17]. In the much larger *VI*ldagliptin expe*R*ience compared wi*T*h sulfonyl*U*rea obs*E*rved during Ramadan (VIRTUE) study enrolling Muslim patients from 10 countries in the Middle East and Asia, significantly fewer patients experienced hypoglycemia with vildagliptin ($n = 684$) (5.4%) compared with SU ($n = 631$) (19.8%) ($P < 0.001$) [33]. These findings are similar to the incidence observed for the hypoglycemic events reported as AEs in the present (VERDI) study (7.5% and 17.9% with vildagliptin and IS, respectively), a smaller study limited to a population originating mostly from the Maghreb region. Patients enrolled in the VERDI study had well-controlled T2DM (mean HbA_{1c} level of 7.2%), and glycemic control did not deteriorate over the short follow-up period in either treatment groups. This is also consistent with findings from VIRTUE, in which the mean HbA_{1c} level was 7.3% and 7.4% in the vildagliptin and SU cohorts, respectively, and changed by −0.24% in the vildagliptin group and +0.02% in the SU group over the course of the study.

Overall, treatment adherence was high in the VERDI study, as only 8.5% of vildagliptin-treated patients and 15.4% of IS-treated patients omitted their treatment ≥5 times

during Ramadan. High treatment adherence with vildagliptin during Ramadan has recently been shown to be better than that reported with SU in the VECTOR study [34]. Treatment adherence was also high overall in the VIRTUE study, but with a similar number of missed doses between cohorts [33]. Besides, compliance to fasting was important in the present study, with patients fasting on average for 29.8 days. Only about one-fourth of patients (21.7% on vildagliptin and 25.6% on IS) reported a temporary diabetes-related interruption of fasting for $\geq$1 day. Conversely, daily consumption of sweets is often increased during Ramadan with iftar, the main meal breaking the fast, being a festive time, but information on total daily food/sugar intake was not collected in the study.

Finally, in the VERDI study, GPs seemed to plan less therapeutic adjustments and treatment modifications for vildagliptin-treated patients during Ramadan, which suggests that physicians are more at ease when prescribing DPP-4 inhibitors in this context of fasting. This is not surprising, in view of the low propensity of DPP-4 inhibitors to cause hypoglycemia.

DPP-4 inhibitors can be considered as an alternative to SUs for vulnerable patients at high risk for hypoglycemia [3, 20]. For instance, the use of DPP-4 inhibitors in the elderly in real-life practice was associated with a lower incidence of hypoglycemic events (6.4%) versus SU or glinides (26%) over 6 months despite a similar improvement in glucose control [35]. Convincing data have started to accumulate for the use of DPP-4 inhibitors in other situations that increase the risk of hypoglycemia such as prolonged fasting during Ramadan [18, 26, 36, 37]. In addition to the data already described with vildagliptin, studies with sitagliptin have been published. In a large, open-label trial in T2DM patients from India and Malaysia, patients were randomized to either remain on their pre-study SU regimen or to switch to sitagliptin 100 mg. Of a total 848 patients, 3.8% of sitagliptin-treated patients ($n = 421$) and 7.3% of the SU-treated patients ($n = 427$) recorded $\geq$1 hypoglycemic events during Ramadan [37]. Similarly, in another open-label, randomized study, 1,021 patients from the Middle East were either switched to sitagliptin or remained on their pre-study SU regimen, and 6.7% of the patients in the sitagliptin group compared with 13.2% in the SU group recorded $\geq$1 event of symptomatic hypoglycemia [36].

The current study has several limitations. The main one was that the collection of hypoglycemic "malaises" was not subjected to mandatory recording on a daily study diary or to systematic supervision. Patients' answers may have had a memory bias, and except for the events that were documented as AEs, the reporting of hypoglycemic episodes was mostly based on recollection. The exact quantification of hypoglycemia remained a hard task because "various" malaises during the long fasting period ($\sim$18 h) over hot summer days may have interfered with the data. Because this non-interventional study aimed at examining real-life practices, SMBG was not requested. In addition, information about the type of SUs used in the study was not collected; however, in France the most widely prescribed SU is gliclazide. Another limitation was that the study had a relatively small sample size and included only French Muslim patients, mostly from the Maghreb region, who were relatively recently diagnosed and had well-controlled T2DM with dual oral therapy. Therefore, results cannot be necessarily extended to the

general Muslim population, who may be using more complex treatment and have more advanced disease.

CONCLUSION

Nevertheless, despite the limitations of the observational methodology, the results were consistent, particularly regarding the data that were better documented (hypoglycemic events reported as AEs, severe episodes, and hypoglycemia leading to unscheduled medical visit) and showed numerically lower frequencies of hypoglycemia with vildagliptin as compared with traditional insulin secretors. In this well-controlled T2DM population fasting for over 18 h/day during hot summer days, GPs planned fewer therapeutic adjustments for vildagliptin-treated patients compared with IS-treated patients prior to Ramadan, suggesting a greater ease with dosing regimens for DPP-4 inhibitors in situations where the risk of hypoglycemia is increased. Given the increasing importance of how best to treat patients with T2DM during Ramadan coupled with the paucity of information available in France, especially from real-life practice, these observations represent a valuable contribution to the existing evidence to help physicians choose between oral antidiabetic drug classes.

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Compliance with ethics guidelines. This observational study was conducted in accordance with the French Privacy Law and respecting the Recommendations for professional standards and good epidemiological practices (ADELF, EPITER, ADEREST, AEEMA 2007). Candidates for inclusion were provided with full information about the study in writing. All data processing was carried out in compliance with the French Information Technology and Privacy Law.

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