"Variations in the pharmacodynamics and pharmacokinetic profiles of different sulfonylureas (SUs) also explain the differences in antidiabetic activity, hypoglycemic risk, selectivity to different tissue-specific SU receptors (SURs), impact on myocardial ischemic preconditioning, and insulin secretion effects. Considering these factors, it may be prudent to select the new SUs that pose lesser threat of hypoglycemia and are cardiac safe."

Sulfonylureas in specific clinical situations: Ramadan

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During Ramadan, management of diabetes is precarious, as it can present substantial risk of hypoglycemia and death when appropriate care is not taken. Focused on the impact of sulfonylureas (SUs) during the month of Ramadan, this article reviews current evidence from different clinical trials and studies with various drugs of this class and the challenges faced by health care practitioners in management of their diabetic patients during this specific period. Since their introduction into clinical practice in the 1950s, SUs have remained the backbone of treatment in the management of type 2 diabetes. Many clinical concerns related to the usage of SUs are drug-specific and do not pertain to the class as a whole. Newer-generation SUs (eg, glimepiride and gliclazide modified release) are supported by abundant evidence, experience, and most notably, outcome statistics, which support the use of SUs in treatment of diabetic individuals. A patient-centered approach — ie, cautious selection of SU, proper dosage, scheduling of administration, and satisfactory counseling of the patient— will ensure that eligible patients are not deprived of the benefits of this well-recognized class of antidiabetic agent. Owing to their effectiveness, safety, and low cost, SUs are a recommended therapy for the treatment of diabetes.

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Sulfonylureas in the management of diabetes

Sulfonylureas (SUs) are one of the oldest groups of oral hypoglycemic agents endorsed by contemporary guidelines for management of type 2 diabetes mellitus (T2DM).[1-5] The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statements recommend use of SU in first-line treatment if metformin is not tolerated, as second-line treatment after metformin, or as an add-on treatment if glycemic goals are not achieved.[6] The Scottish Intercollegiate Guidelines Network (SIGN), the International Diabetes Federation (IDF), and the National Institute for Health and Clinical Excellence (NICE) guidelines also recommend SUs as first- or second-line agents in patients who are not overweight, in those who have an intolerance or contraindications to metformin, and in those needing a quick response due to signs and symptoms of hyperglycemia.[1,4,5]

An optimal oral hypoglycemic agent should provide glycemic control with low risk of adverse effects while providing low-cost ease of use.[7] SUs are well-recognized for blood glucose control and act on pancreatic β-cells to stimulate insulin secretion. Since the introduction of tolbutamide in 1956,[8] different SUs have been marketed, generally categorized on the basis of their affinity of binding with SU recep-

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tors (SURs).[9] The introduction of new SUs (eg, glimepiride, gliclazide modified release [MR]) with fewer side effects and improved effectiveness[10] have bolstered their reputation.[11-14]

SUs are insulin secretagogues that encourage endogenous insulin secretion by inhibiting adenosine triphosphate–sensitive potassium (K_{ATP}) channels on pancreatic β-cells via binding to the SUR subunit on the β-cell plasma membrane.[15] SUs attach to a common SUR subunit on β-cells, shutting down the K_{ATP} channels and inhibiting K^+ efflux, subsequently depolarizing the membrane and enabling entry of Ca^{2+} ions. Consequently, exocytosis of insulin secretory vesicles is encouraged.

However, SUs do not all act the same way. Glimepiride encourages insulin secretion by binding to a specific 65-kDa receptor protein site on the K_{ATP} channel of pancreatic β-cells and causes inhibition of the SUR subunit.[16,17] Compared with glibenclamide, glimepiride has lesser binding attraction (2- to 3-fold) for SUR, as well as a greater rate of onset (2.5- to 3-fold) and offset (8- to 9-fold) of drug binding to the receptor.[16,18] Gliclazide also shows selective binding of the SUR1 receptor, resulting in a cascade of intracellular events that is similar to that induced by glucose. Gliclazide is unique among the SU class regarding its mechanism of insulin exocytosis, as it is the only SU that does not bind to Epac2 (exchange protein directly activated by cAMP 2), a stimulating factor of insulin exocytosis. As a consequence, by not binding to Epac2, gliclazide does not overstimulate insulin release, leading to a very low risk of hypoglycemia.[19]

Variations in the pharmacodynamics and pharmacokinetic profiles of different SUs also explain the differences in antidiabetic activity, hypoglycemic risk, selectivity to different tissue-specific SURs, impact on myocardial ischemic preconditioning, and insulin secretion effects.[20] Considering these factors, it may be prudent to select the new SUs that pose lesser threat of hypoglycemia and are cardiac safe. However, a dearth of head-to-head data from clinical studies requires cautious evaluation of SUs concerning patient-pertinent end points.[21]

SELECTED ABBREVIATIONS AND ACRONYMS

CREED	Multi-country Retrospective Observational Study of the Management and Outcomes of Patients with Type 2 Diabetes During Ramadan in 2010 [study]
EPIDIAR	EPIdemiology of DIAbetes and Ramadan [study]
FPG	fasting plasma glucose
GLIRA	GLimepiride In RAmadan [study]
MR	modified release
READ	Ramadan Education and Awareness in Diabetes [study]
SU	sulfonylurea
SUR	sulfonylurea receptors
T2DM	type 2 diabetes mellitus

Use of sulfonylureas during Ramadan

Current new-generation SUs, such as gliclazide MR and glimepiride, are comparatively safer and effective for use during Ramadan.[22,23] South Asian guidelines actually endorse these newer SUs as an effective, safe, and economical preference during Ramadan fasting.[24] A clinical trial in well-controlled Asian T2DM patients showed that monotherapy with gliclazide MR in the evening during Ramadan, taken at the main meal after sunset (Iftar), can safely maintain glycemic control with fewer hypoglycemic incidents during the Ramadan fasting period.[23] Similar results were witnessed with glimepiride.[22] Therefore, use of these contemporary SUs with a clinician-directed dosing regimen is recommended in T2DM patients fasting during Ramadan.[24]

Epidemiology

Out of 193 countries on the United Nations list,[25] 57 are predominantly Muslim, a population of approximately 2.08 billion or about 25% of the global population.[26] Most of these Muslim countries (62%) are located in the Asia-Pacific region, 20% are in the Middle East and North Africa, 16% are in Sub-Saharan Africa, and about 2% are in Europe and the Americas. IDF statistics from 2015 revealed that there were about 415 million people with diabetes globally, which was estimated to reach 642 million by 2040, a 55% increase.[27]

Incidence of diabetes shows geographic disparities worldwide with a worrisome evolving rise in the Middle East, Western Pacific, Sub-Saharan Africa, and South-East Asia, where 10% of adults may be diabetic. As regards the prevalence of diabetes in the adult population, the Middle East and North African countries have the highest occurrence rate, 10.9%.[27] On closer inspection of this epidemic, it is evident that more than 90% of Muslims are living in these areas. Furthermore, the IDF 2014 data revealed that 80% of individuals with diabetes were residing in low- and middle-income nations, with the socially disadvantaged being the most susceptible.

On the basis of an 8.3% global pervasiveness of diabetes in adults—coming to roughly 382 million individuals[27]—together with evidence from the population-centered EPIDIAR study (EPIdemiology of DIAbetes and Ramadan) showing that 43% of patients with type 1 diabetes (T1DM) and 79% with T2DM fast during Ramadan,[28] it can be concluded that globally, about 40-to-50 million diabetic individuals fast during Ramadan. Merging EPIDIAR statistics with the latest approximations for the global Muslim population and overall diabetes prevalence suggests that there are 148 million Muslims across the world with diabetes, and 116 million of them may fast during Ramadan. Data from the CREED study (Multi-country Retrospective Observational Study of the Management and Outcomes of Patients with Type 2 Diabetes During Ramadan in 2010) showed that 94.2% of Muslims with T2DM who fast during Ramadan do so for at least 15 days, and some of them fast daily.[29] It has also been recognized that more than 20%

of Muslims with diabetes fast outside Ramadan practices. In the same study, 40% of patients with T1DM and 35% of patients with T2DM were categorized by their physicians as having a high or very high risk of experiencing complications during Ramadan.[29]

The Muslim population is spread extensively throughout the world, and some are fortunate enough to have access to diabetes mellitus management, including health care specialists with an understanding of the fasting protocols, medication regimens that are modified in accordance with the patients' clinical profiles, and Ramadan-focused diabetes counseling.[30] In contrast, patients in poor countries or underprivileged and inaccessible populations face huge challenges with regard to the suitability and provision of health care, availability of prescriptions, and issues with storing of medications. This is in addition to problems associated with providing essential Ramadan-focused diabetes counseling.

Ramadan

For all Muslim adults, fasting during Ramadan is one of the five pillars of Islamic practices. The Holy Quran specifically exempts the sick from the mandatory fasting during the month of Ramadan. Patients with diabetes fall under this category because their chronic metabolic disorder may place them at high risk for various complications.

Ramadan is a lunar-based month and its duration varies between 29 and 30 days, and the fasting month is brought forward by about 10 days each year, which means that over time the season in which Ramadan falls continues to change. This type of fasting is defined as periodic food and water deprivation during daylight hours with free access during the night for the duration of one lunar month. Depending on the geographical location and season, the duration of the daily fast may range from 12 to 20 hours. For diabetics, the main effects of Ramadan are on diet, daily activity, and medications.

Physiological changes and risks associated with Ramadan fast

During Ramadan, the number of meals is reduced to two, one large meal at sunset and one before dawn, ie, Iftar and Suhoor respectively. Along with changes in number, timing, and calorie content of the meals, the composition of the meal is disturbed as well. During Ramadan, there is more consumption of fried foods and carbohydrates in the form of dates, juices, and especially sweet foods. Moreover, daily activity is generally reduced during the daytime because of fasting and increased during the night. Among otherwise healthy nondiabetic people during the fast, circulating glucose levels tend to fall, leading to decreased secretion of insulin. Simultaneously, the levels of glucagon and catecholamines rise, which stimulates glycogenolysis and gluconeogenesis. However, in patients with diabetes, this mechanism is disturbed because of the underlying pathophysiology and the effects of pharmacological agents. Serious risks of fasting include hypoglycemia, hyperglycemia, and dehydration. Prolonged fasting in the absence of adequate insulin can lead to excessive glycogenolysis, gluconeogenesis, and ketogenesis, leading to hyperglycemia and ketoacidosis. The EPIDIAR study[28] found that the change in eating patterns during Ramadan is associated with a 4.7-fold increased risk of severe hypoglycemia in T1DM patients and a 7.5-fold increased risk in T2DM patients. Severe hypoglycemia was more frequent in patients with changes in dosage of oral hypoglycemic agents or insulin and those with a significant change in lifestyle.[28] In another study, hypoglycemia was reported to occur in up to 20% of SU-treated patients who were fasting during the month of Ramadan,[31,32] but other studies failed to report a significant increase in the frequency of hypoglycemia during Ramadan among patients treated with oral hypoglycemic medications or insulin.[32,33] The EPIDIAR study[28] also showed a 5-fold increase in the appearance of severe hyperglycemia during Ramadan in patients with T2DM and an approximately 3-fold increase in the occurrence of severe hyperglycemia with or without ketoacidosis in patients with T1DM.[28] Patients with diabetes, especially those with T1DM, are at an increased risk for development of diabetic ketoacidosis, particularly if they are grossly hyperglycemic (uncontrolled diabetes, with high glycated hemoglobin level [HbA_{1c}]) before Ramadan.[28,34]

Restriction of fluid intake during the fast, especially if prolonged, can cause dehydration that may become worse in hot and humid climates and among individuals who perform hard physical labor.[35] Furthermore, contraction of the intravascular space may also contribute to a hypercoagulable state in diabetic patients already known to have high levels of clotting factors, decreased endogenous anticoagulants, and impaired fibrinolysis.[36] Increased blood viscosity secondary to dehydration may also enhance the risk of cerebral venous sinus thrombosis,[37] stroke, and retinal vein occlusion.[38]

Current clinical practice guidelines for the management of diabetes during Ramadan

The READ study (Ramadan Education and Awareness in Diabetes),[39] was a retrospective study in the United Kingdom that assessed the safety of Ramadan fasting among Muslims with T2DM who joined an organized instructive program, which included counseling about physical activity, meal arrangement, glucose checking, hypoglycemia (defined as home blood glucose <63 mg/dL, 3.5 mmol/L), and dosing and scheduling of medication. The study revealed a significant decrease in total episodes of hypoglycemic incidents among individuals attending the program. Hence, counseling before the period of Ramadan seems to be a fundamental step in averting undesired hypoglycemia.

Professional judgment would suggest that should a patient signal a desire to fast, the initial step would be to perform a risk categorization.[40] Patient education specifically about diabetes

is extensively discussed to be the foundation of care, and education about self-supervision of diabetes management has been shown to be effective in reducing complications.[41] However, appropriate diabetes education in many low- and middle-income Muslim states is very limited, and in rural areas of unindustrialized countries, it is not available.[37] Patients who fasted during Ramadan without having received structured educational counseling about diabetes management during this period had an increase in hypoglycemic episodes, whereas those who did have such educational counseling had a substantial decrease in hypoglycemic incidents.[42]

Sulfonylurea

SUs are insulin secretagogues and have been shown to increase hypoglycemia risk. However, statistics on SU use during Ramadan are inconsistent. GLIRA (GLimepiride In RAmadan), which was a prospective observational study including 332 patients (from six countries), has demonstrated that the hypoglycemia risk and glycemic effect of glimepiride used before Iftar is comparable to that observed before the period of Ramadan.[22] An additional study performed on 136 male patients taking gliclazide MR 60 mg revealed that moving the time of medication intake to Iftar does not result in an increased risk of hypoglycemia.[23] Furthermore, an observational study including 1378 patients (from five countries) in which a SU was given either as a single agent or with metformin has reported at least one hypoglycemic event in 19.7% of cases.[43] Risk of hypoglycemic episodes with glibenclamide, glimepiride, and gliclazide were 25.6%, 16.8%, and 14% respectively. The overall risk of severe hypoglycemia was 6.7% among patients using SUs during Ramadan fasting. The greatest risk was reported with glibenclamide (10.8%), whereas the lowest risk of severe hypoglycemia was with gliclazide (2.6%). In another study, the risk of symptomatic hypoglycemia was found to be considerably higher; that study included 1066 patients randomized to sitagliptin and SU treatment groups during Ramadan. The risk was greater with glibenclamide than glimepiride and gliclazide, in accordance with the previous study (risk: 19.7%, 12.4%, and 6.6% respectively).[44] Consequently, SU use in Ramadan is accompanied by an increased risk of hypoglycemia, and distinctive patient groups (elderly patients, patients who have had hypoglycemia associated with SUs, and those who are consuming high-risk hypoglycemic SUs like glibenclamide) may benefit from drug modification. Those on intermediate-risk SUs, using glibenclamide, may benefit from replacement with gliclazide. Those patients who have HbA_{1c} levels under 7.5% before Ramadan are advised to decrease the drug dosage.[45] The recommended medication process for consumers of single-dose, long-acting SU is to take the morning dose at Iftar; those with a twice daily dosage are recommended to switch the morning dose to Iftar and to start half of the evening dose at Suhoor.[46] In regard to these oral hypoglycemic agents, the collective wisdom suggests avoiding them as much as possible because of the risk of hypoglycemia.[47] Short-acting insulin secretagogues—meglitinides—appear to be more beneficial than long-acting SUs in terms of hypoglycemia during Ramadan. One study has compared the efficacy and consistency of glargine, glimepiride, and repaglinide treatment and showed no substantial differences between them.[33] However, two diverse studies have recounted fewer hypoglycemic incidents with repaglinide than glibenclamide.[48,49] Furthermore, an observational study on this aspect has shown that preprandial repaglinide with insulin glargine does not result in an increased risk of hypoglycemia during Ramadan.[50] Although meglitinides are less associated with hypoglycemia than SUs, the possibility of this occurring should still be taken into consideration and meglitinides thus prescribed before Iftar and Suhoor.

SUs and other insulin secretagogues remain a treatment modality during Ramadan in spite of potential for hypoglycemia and weight gain consequences. Our database search revealed four small clinical trials relevant to this.[23,33,51,52] The study described by Zargar et al[23] evaluated whether moving the administration of an extended-action SU, gliclazide MR, to the evening during the 29 days of Ramadan can sustain glycemic control in patients with T2DM. Male T2DM patients from Bangladesh, Pakistan, and India, under glycemic control with gliclazide MR 60-mg monotherapy, changed their medication schedules so that they received the dose in the evening, and then after Ramadan they returned to the morning administration schedule. The main outcome of the study was the difference in fasting plasma glucose (FPG) before and after Ramadan. In 136 patients, mean (95% confidence interval [CI]) FPG reduced by 0.01 mmol/L (0-0.2; P=0.3) with evening prescription by the end of the fast and increased by 0.2 mmol/L (0.1-0.3; P=0.01) after reverting to morning administration 20 days later. There were five (3.7%) hypoglycemic episodes before, three (2.2%) during, and two (1.5%) after Ramadan. The investigators determined that male T2DM patients undertaking the Ramadan fast can safely obtain glycemic control with evening administration of gliclazide MR 60 mg during the fast, reverting to a morning schedule thereafter. However, a recent meta-analysis review of randomized controlled trials compared the effect of switching patients from SUs to dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin or vildagliptin), looking into the risk of hypoglycemia. That review concluded that both gliclazide and DPP-4 inhibitors are associated with low risk of hypoglycemia during Ramadan fasting.[53] Another study compared the effect of vildagliptin or gliclazide as an add-on to metformin on hypoglycemia risk and body weight during Ramadan fast. It found no statistically significant difference in hypoglycemia episodes (P=0.173) and body weight reduction (P=0.423) between vildagliptin and gliclazide treatment.[54]

Conclusion

SUs are the mainstay of treatment in the supervision of patients with T2DM. The well-recognized glycemic effectiveness, safety, and acceptability of SUs support their use as an essential

part of diabetes treatment. Given the fact that many of the clinical apprehensions associated with the use of SUs are drug-specific and do not relate to the class as a whole, the possibility to carefully select a particular SU for treatment should be considered advantageous. Appropriate patient selection, optimal choice of drug and dose, education and counseling of the patient, and education of the physician will help ensure the effective and safe use of this essential class of drugs.

Clinical data confirm that patients with T2DM may continue to use newer-generation SUs and to fast safely during Ramadan. The use of older drugs within this class, such as glibenclamide, should be avoided in favor of gliclazide and glimepiride, which carry a much lower risk of hypoglycemia. The use of these drugs should be individualized through clinician guidance and medication adjustments.

Studies have demonstrated that without proper guidance, diabetic patients that fast during Ramadan can disrupt control of their blood glucose levels and may be susceptible to consequent risks. The physician's obligation in such circumstances is to assess the patients. It is important to appropriately educate diabetic patients about fasting during Ramadan and to make necessary changes in their treatment regimens to minimalize risks. During Ramadan, patients must remain in close contact with their physician, diabetes nurse, and dietitian.

Presuming glycemic control is acceptable on the current treatment regimen just before Ramadan, it is recommended that the timing of SU administration is reversed so that the morning dose is taken with Iftar in the evening and the evening dose taken with Suhoor before dawn, with the mid-day dose, if any, omitted. The Suhoor dose may be reduced to around 50% of the dose used just before Ramadan.

The IDF's latest diabetes and Ramadan practical guideline recommendations for SU dose adjustments in people with T2DM are as follows: (i) for patients on once-daily dosing, that dose should be taken at Iftar; however, in patients with well-controlled blood glucose levels, the dose may be reduced; (ii) for patients on twice-daily dosing, the Iftar dose remains the same; in patients with well-controlled blood glucose levels, the Suhoor dose should be reduced; (iii) older drugs in the class—eg, glibenclamide—carry a higher risk of hypoglycemia and should be avoided; and (iv) newer-generation SUs (gliclazide, glimepiride) should be used in preference.[55] ■

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