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# Sulfonylureas-associated cardiovascular disease and beta-cell dysfunction – is It time to dispel the myth?

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## ABSTRACT

The evidence regarding sulfonylureas glucose-lowering efficacy is robust; furthermore, they are convenient and their out-of-pocket cost is in the range of many other diabetes medications. Sulfonylureas can cause weight gain, and particularly if used inappropriately, hypoglycemia. Furthermore, some studies have related their use to adverse cardiovascular outcomes, including mortality. In addition, sulfonylurea-associated induced beta-cell dysfunction has been proposed as one of the most important disadvantages related to their use. On the other hand, hypoglycemia is related to death, cardiovascular events, myocardial infarction, stroke, cognitive impairment, dementia, impaired autonomic function, fall-related fractures, poor quality of life, and increased health-care costs. These adverse outcomes seem to be related more to episode(s) of hypoglycemia *per se* rather than to the use of sulfonylureas or a particular anti-hyperglycemic drug class. In addition, across studies, data associating sulfonylureas

## RESUMEN

Existe evidencia extensa de que las sulfonilureas son eficaces como hipoglucemiante oral; además, su conveniencia y bajo costo les permite competir con otros tratamientos de diabetes actuales. Las sulfonilureas pueden causar ganancia de peso e hipoglucemias (por uso inadecuado). Además, algunos estudios han relacionado su uso a eventos cardiovasculares adversos, incluyendo mortalidad. Adicionalmente, la propuesta de disfunción de célula β mediada por sulfonilureas es una de las mayores limitantes para su uso. Por otra parte, la hipoglucemia se ha relacionado con mortalidad, eventos cardiovasculares, infarto de miocardio, accidentes cerebrovasculares, discapacidad cognitiva, demencia, disfuncionalidad autonómica, fracturas por caídas, pobre calidad de vida e incremento en los costos de los servicios de salud. Estos desenlaces desfavorables parecen relacionarse más con episodios de hipoglucemia *per se* que al uso de las sulfonilureas o de algún otro hipoglucemiante

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with adverse cardiovascular events, including death, remains imprecise, and inconsistent. Likewise, the pancreatic beta-cell function is modified by many factors, and its relation with sulfonylureas remains open to debate. Hence, when choosing a diabetes drug, patients and clinicians should discuss differences between glucose-lowering medications in terms of benefits, harms, cost, and convenience. In this patient-centered discussion, sulfonyl ureas should be included as one of the evidence-based available options. (REV MEX ENDOCRINOL METAB NUTR. 2017;4:130-6)

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específicamente. Adicionalmente, los estudios que asocian las sulfonilureas con eventos cardiovasculares adversos (incluyendo mortalidad) son imprecisos e inconsistentes. Igualmente, diversos factores modifican la funcionalidad célula β pancreática haciendo debatible su relación con las sulfonilureas. Por consiguiente, en el momento de elegir, pacientes y médicos deberían discutir las diferencias de los medicamentos hipoglucemiantes en términos de beneficio, daño, costos y conveniencia, considerando a las sulfonilureas como parte de las opciones para el manejo de diabetes centrado en el paciente.

**Palabras clave:** Diabetes. Sulfonylureas. Hypoglycemia. Disfunción de célula β.

## BACKGROUND

The goals of diabetes care are to reduce the patients' risk of acute and long-term complications, increase their lifespan, and improve their health-related quality of life. Relying on evidence that stems from pivotal trials, tight glycemic control (hemoglobin A1c [HbA1c] ≤ 7.0%) has been the usual approach to reach these goals[1,2]. To achieve this, clinicians and patients with diabetes now have a vast number of treatment alternatives[3]. This, while exciting and flexible, also imposes the caveat of having the certainty of which medication is best for each patient. These challenges arise from inconsistencies in the body of evidence regarding the benefits, convenience, costs, and particularly adverse effects (i.e., hypoglycemia and weight gain)[4-6].More than 50 years ago, sulfonylureas revolutionized diabetes treatment by being the first class of glucose-lowering oral medications available to treat Type 2 diabetes. The evidence regarding their glucose-lowering efficacy (HbA1c reduction) is robust, they are convenient (i.e., oral, once or twice daily), and their out-of-pocket cost is in the range of many other diabetes medications[7]. Due to the intrinsic mechanism of action of sulfonylureas (i.e., increasing insulin secretion from pancreatic beta-cells), they can cause hypoglycemia and weight gain[8]. The augmented risk of hypoglycemia with sulfonylurea treatment is higher when used inappropriately (Table 1). In addition, in some observational studies, sulfonylureas have been related to an increased risk of hypoglycemia and cardiovascular disease and death[9-13]. Moreover, sulfonylurea-associated induced beta-cell dysfunction and consequent escalation to a more complex treatment regimen (including insulin) have been proposed as important disadvantages to their use, particularly now that many other glucose-lowering drugs are available that spare patients from these undesirable risks[14-16]. This has caused other glucose-lowering medications to be recommended by clinical guidelines over sulfonylureas, and sulfonylurea use has decreased considerably[2,17,18]. Yet, these assumptions remain open to debate[19]. Thus, to better understand these controversies, we decided to conduct this review with the objective to clarify the evidence regarding sulfonylureas adverse events, particularly hypoglycemia, cardiovascular outcomes, and beta-cell dysfunction.

## HYPOGLYCEMIA AND UNFAVORABLE HEALTH-RELATED OUTCOMES

Severe hypoglycemia (i.e., an episode that requires assistance from a third-party) is associated with important unfavorable patient outcomes such as death, cardiovascular events (e.g., myocardial infarction and stroke), cognitive impairment, dementia, impaired autonomic function, fall-related fractures, poor quality of life, and increased costs[20-25]. *De facto*, even mild hypoglycemic episodes, which have been largely overseen and are difficult to detect by most trials, impose an acute burden, distress, and disruption in the ability of patients to perform everyday activities[26]. Thus, for most patients, hypoglycemia is an undesirable aspect of treatment, and its prevention and prompt management is a sign of high-quality diabetes care.

## Sulfonylureas and hypoglycemia risk

Hypoglycemia is the most common adverse event caused by sulfonylureas; however, when properly used, it remains rare (Table 1). In the UK Prospective Diabetes study (3 years' follow-up) at least one event of any type of hypoglycemia was reported in around 15% of the patients taking chlorpropamide and in 25% taking glibenclamide. Severe hypoglycemia (third-party assistance and hospitalization) was reported to be about 3% in both groups[27]. More recently, a systematic review and meta-analysis of 22 randomized clinical trials (RCTs) with a duration of at least 3 months reported mild episodes of hypoglycemia with sulfonylureas in around 10% of the cases and severe episodes in 0.8%[9]. Furthermore, Monami et al. reported in another meta-analysis of RCTs (≥ 24 weeks of duration [mean duration 69 weeks] and including 19,801 patients) that the risk of severe and mild hypoglycemia with sulfonylureas had a three-fold increase when compared to any other oral medication[10]. Of note, while similar glycemic control second and third generation sulfonylureas (e.g., glipizide, glimepiride, gliclazide) have been demonstrated to reduced the risk of hypoglycemia odds ratio (OR) 1.9 (95% confidence interval [CI]: 1.2-2.9) when compared to first generation (OR 16.6 [95% CI: 13.2-19.9] and OR 3.5 [95% CI: 1.2-5.9]) (e.g., tolbutamide, chlorpropamide)[28]. For instance, in a systematic review, gliclazide was found to have a reduced risk of mild and severe hypoglycemia (1.4% [95% CI: 0.8-2.4%]) and 0.1% (95% CI: 0-0.7%), respectively when compared to other sulfonylureas and insulin[9].

## Sulfonylureas and cardiovascular risk

In addition to the burden than an episode of hypoglycemia imposes, a direct relationship between sulfonylurea use and all-cause mortality and adverse cardiovascular outcomes has been reported. Tolbutamide was the first sulfonylurea associated with mortality in the University Group Diabetes Study; however, the results of this trial were dispelled by the UK Prospective Diabetes Study, which demonstrated no effect of sulfonylureas regarding cardiovascular outcomes[11,14]. Later, Kheirbek et al., in a retrospective analysis of almost 18,000 US veterans with Type 2 diabetes, reported that glibenclamide (OR: 1.80, 95% CI: 1.51-2.14), glipizide (OR: 1.56, 95% CI: 1.33-1.83), and chlorpropamide (OR: 3.02, 95% CI: 1.09-8.35) increased the risk of all-cause mortality[12]. Insulin and rosiglitazone were also related to this association. Moreover, in a systematic review of 115 RCTs (62 trials reporting data on major cardiovascular events), sulfonylureas were found to significantly increase all-cause mortality (OR: 1.22, 95% CI: 1.01-1.49), yet there was no difference compared to other glucose-lowering agents in the risk of stroke or myocardial infarction[13]. Recently, Azoulay and Suissa in a systematic review of observational studies reported that sulfonylureas were associated with an increased risk of cardiovascular events and mortality when compared to metformin; however, some of the studies were at high risk of bias[29]. On the other side of the spectrum, some studies have not found an association between sulfonylurea use and adverse cardiovascular outcomes. In a Danish population-based study involving more than 56,000 patients with Type 2 diabetes, ratios of all-cause mortality, cardiovascular death, and a composite of myocardial infarction, stroke, and cardiovascular death were not significantly different between metformin-glimepiride as compared to glibenclamide (OR: 0.98, 95% CI: 0.87-1.10), gliclazide (OR: 1.01, 95% CI: 0.88-1.15), repaglinide (0.81, 95% CI: 0.62-1.05), or tolbutamide (1.04, 95% CI: 0.85-1.28)[30]. Moreover, in this study, glipizide was associated with an increased risk of all-cause and cardiovascular mortality (1.21, 95% CI: 1.01-1.46, p

Table 1. Situations in which sulfonylurea-induced hypoglycemia is more frequent and where special attention and education should be pursued

- After a missed meal
- Patients also using insulin as part of their treatment regimen
- Exercise (increase in intensity or not planned)
- Impaired renal, cardiac, or gastrointestinal function
- Inadequate and variable dose and/or frequency of administration
- Malnutrition
- Alcohol abuse
- After being discharged from hospital
- Concurrent use of warfarin, sulfonamides, and gemfibrozil

= 0.04). In a systematic review that included 21 sulfonylurea RCTs, glibenclamide was associated with a 52% increase in the risk of at least one episode of hypoglycemia when compared to other secretagogues and 83% when compared to other sulfonylureas; however, no effect on mortality or cardiovascular events was observed[31]. Similarly, a systematic review that included 47 RCTs (with at least 52 weeks of duration) of the second and third generation sulfonylureas reported that the latter was not associated with all-cause (OR: 1.12, 95% CI: 0.96-1.30) or cardiovascular mortality (OR: 1.12, 95% CI: 0.87-1.42), myocardial infarction (OR: 0.92, 95% CI: 0.76-1.12), or stroke (OR: 1.16, 95% CI: 0.81-1.66)[32]. Moreover, a recent network meta-analysis that involved more than 300 RCTs, reported no difference between the nine glucose-lowering drug classes (including sulfonylureas) in the primary outcome of the study (cardiovascular mortality). The risk of myocardial infarction, stroke, or amputations was also not different despite an increased risk of hypoglycemia with sulfonylureas and insulin[33]. In addition, Zeller et al. showed in a French nationwide population-based study that, in patients with a recent episode of myocardial infarction, previous glimepiride and gliclazide use was associated with lower rates of mortality and complications (OR: 0.15; 95% CI: 0.04-0.56)[34]. Finally, Simpson et al. demonstrated in a systematic review and network meta-analysis that gliclazide 0.65 (95% CI: 0.53-0.79) and glimepiride 0.83 (95% CI: 0.68-1.00) were associated with a lower risk of all-cause mortality and cardiovascular-related mortality when compared to glybenclamide[35].

There are several factors that can explain the inconsistencies in the reported outcomes across the studies and that reduce the confidence in the association. First, the trials that have informed about the relationship have done so considering that hypoglycemia was not the primary outcome for which the study was designed (i.e., usually focused on efficacy [HbA1c reduction])[36,37]. Second, in most studies sulfonylureas have been classified as a group, rather than individually. While this can be the case for many other glucose-lowering drug classes, sulfonylureas have important differences between them in terms of pharmacokinetics and mechanism of action (i.e., selective sulfonylureas [glimepiride and gliclazide] for pancreatic receptors and not for cardiac receptors appear to be safer than other sulfonylureas). Indeed, in a retrospective cohort study including over 11,000 patients with Type 2 diabetes and documented cardiovascular disease, sulfonylureas as monotherapy (glipizide, glibenclamide, or glimepiride) were not associated with an increased risk of overall mortality (hazard ratio [HR]: 1.36, 95% CI: 0.96-1.91 and HR: 1.39, 0.99-1.96)[38]. Third, sulfonylureas are used late in the progression of the disease, and particularly in some observational studies cases allocated to receive sulfonylureas are more complex (i.e., more comorbidities and chronic diabetes complications), and hence is very difficult to assess if the higher rates of adverse cardiovascular outcomes are attributable to the treatment *per se* or the patient profile. Forth, most of the data that embrace this association stems from retrospective population-based studies. In these studies, researchers take advantage of large databases that comprise most but not all patients treated for Type 2 diabetes. At the time of the study, neither patients nor clinicians were aware of any research question, and hence, instead of having systematically determined outcomes, only limited endpoints can be ascertained as a result of laboratory tests (e.g., HbA1c, low-density level-cholesterol, albuminuria) or treatment results (e.g., mortality, cardiovascular events). This means that important patient outcomes (e.g., quality of life, mild episodes of hypoglycemia) can be missed or lack thorough documentation if this was indeed the case. Moreover, clinician's choice (chance), rather than random allocation, was the reason for each medication prescription, and when the drug choice is tied with patient prognosis, intrinsic bias reduces confidence in the estimates[37,39]. Complex statistical methods and adjustment of confounders (e.g., age, comorbidities, time of diabetes diagnosis) can reduce but never eliminate the residual confounding factors. Hence, the body of evidence linking sulfonylureas with adverse cardiovascular outcomes remains uncertain and in the need of further studies.

## Sulfonylureas and beta-cell dysfunction

To date, there are 11 known pathogenic factors that play a role in the physiopathology and progression

of Type 2 diabetes[15]. All of these physiopathological factors are well recognized and important; however, the pace and advancement of pancreatic beta-cell dysfunction are paramount elements in the progression of Type 2 diabetes[16]. Even though in early phases of diabetes insulin secretion is increased, this does not mean that pancreatic beta-cells are functioning properly. In fact, it is well recognized that by the time Type 2 diabetes is diagnosed, around 80% of pancreatic beta-cell function is already lost[16]. One of the factors associated with beta-cell dysfunction is the use of sulfonylureas, yet, there are other evidence-based factors that might play a role: (a) age: it is well known from numerous studies that advancing age is related to a decline in beta-cell function[40-43]; (b) genes: studies in first-degree relatives demonstrate a clear relationship (particularly *TCF7L2*)[44-46]; (c) insulin resistance in pancreatic beta-cells: while the exact mechanism remains unclear, lipid deposition in beta-cells and hypersecretion of islet amyloid polypeptide have been linked to the beta-cell malfunction[47]; (d) lipotoxicity and glucotoxicity: elevated plasma free fatty acids and chronic glucose elevation *per se* impair insulin secretion[48]; (e) islet amyloid polypeptide: its hypersecretion and deposition in pancreatic beta-cells has been related to the progressive dysfunction of insulin secretion[49,50]; and (f) glucagon-like peptide 1 deficiency and gastric inhibitory polypeptide resistance[51,52]. Hence, although sulfonylureas have been associated with beta-cell dysfunction, it is clear that there is evidence of many other factors that are well known to affect normal pancreatic beta-cell function.

The first association between sulfonylureas use and pancreatic beta-cell dysfunction stems from the results of the UKPDS trial[14]. In this trial, it became clear that by the 3rd year most of the participants needed an add-on medication as beta-cell dysfunction progressed, an inference that was made indirectly from a continuous increase in HbA1c. However, this was not only observed in patients randomized to the sulfonylureas arm (chlorpropamide, glibenclamide, and glipizide) but also in the metformin group. The most robust evidence of this association; however, emerges from the ADOPT study, a trial in 4360 patients with recently diagnosed Type 2 diabetes naive to medications, that had the primary objective of time to monotherapy failure (defined as confirmed fasting plasma glucose > 180 mg/dL) between glibenclamide, metformin, and rosiglitazone[53]. The cumulative incidence of monotherapy failure was reported to be 34% with glibenclamide, 21% with metformin, and 15% with rosiglitazone. HbA1c increased in all three groups (0.42% HbA1c difference between rosiglitazone and glibenclamide), and these two factors were taken as indicators of beta-cell dysfunction. However, when the beta-cell function was determined by homeostasis model assessment 2, the latter was significantly increased in the glibenclamide group (1.45; 95% CI: 1.42-1.48) during the first 6 months when compared to metformin (1.16, 95% CI: 1.14-1.19) and rosiglitazone (1.17, 95% CI: 1.15-1.19). After that, a progressive decrease in beta-cell function was observed in all three groups, showing no difference at the end of the study between sulfonylureas and metformin or rosiglitazone. The authors reported a more profound annual rate decline with sulfonylureas, but this was only because of the initial beta-cell function increase with sulfonylureas, and hence, did not represent a true state of beta-cell dysfunction. In fact, in a rodent model, hyperglycemia management with intensive insulin therapy restored the sulfonylurea glucose-sensitive insulin secretion of pancreatic beta-cells[54]. Furthermore, using beta-cell islets, Del Guerra et al. demonstrated that sulfonylureas significantly induced expression, at both genes and protein levels of pancreatic and duodenal homeobox protein 1 (differentiation transcription factor) and Ki-67 a marker of proliferation[55]. In addition, it has been shown that lipotoxicity, particularly affects the first phase of insulin secretion in response to glucose but remained preserved after stimulation with sulfonylureas[56]. Finally, in a cultured pancreatic beta-cell line gliclazide did not an affect either intracellular reactive oxygen species production or the numbers of apoptotic cells when compared to other sulfonylureas which suggests that it may have a benefit in the preservation of functional beta-cell mass. Consequently, with this data, it is clear that the association of sulfonylureas with beta-cell dysfunction remains ambiguous and lacks a strong evidence-based association - hopefully the future studies can reduce this knowledge gap.

## CONCLUSION

Hypoglycemia is related to adverse patient outcomes, and its avoidance remains a paramount aspect of diabetes management to avoid. These adverse outcomes seem to be related more to the hypoglycemia event *per se* rather than with a particular class of hypoglycemic agent. While sulfonylureas glucose-lowering capacity is robust they increase the risk of hypoglycemia; however, more often if used inappropriately and lower with second or third generation sulfonylureas. The body of evidence linking sulfonylurea-associated hypoglycemia with adverse cardiovascular outcomes is still sparse and inconsistent across studies, which reduces the confidence of a cause-effect. Likewise, the pancreatic beta-cell function is affected by many known factors and its direct impairment due to sulfonylureas remains uncertain to date. In the interim, a patient-centered approach, such as shared decision-making, in which patients and clinicians discuss the research evidence (pros and cons) regarding the available glucose lowering options (in which sulfonylureas should be included as one of the evidence-based available options) while also considering the values, preferences, and context of the patient. With the hope that the treatment plan fits and accommodates better into the patient's life.

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## CONFLICTS OF INTEREST

RRG reports personal fees from Sanofi Aventis outside the submitted work. PAV reports personal fees from Boehringer-Inhelheim, Janssen, and Sanofi Aventis outside the submitted work, RAG reports personal fees from Sanofi Aventis, Novo Nordisk, Eli Lilly, and Boehringer-Inhelheim outside the submitted work, RCR reports personal fees from Eli Lilly, Janssen, Astraseneca, and Sanofi Aventis outside the submitted work, HLM reports personal fees from Novo Nordisk, Janssen, Astrazeneca, Roche, and Sanofi Aventis outside the submitted work, JRG reports personal fees from Sanofi Aventis outside the submitted work, RVO reports personal fees from Sanofi Aventis, Eli Lilly, Janssen, and AstraZeneca outside the submitted work.

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## SEARCH STRATEGY AND SELECTION CRITERIA

We conducted a comprehensive search of the following databases: PubMed (MEDLINE), Ovid EMBASE, Web of Science, and Scopus. Search terms "diabetes," "hypoglycemia," "sulfonylureas," "cardiovascular disease," and "beta-cell dysfunction" were used to identify articles (RCTs, systematic reviews and review articles) published up to January 01, 2017, that focused on hypoglycemia and beta-cell dysfunction particularly related to sulfonylurea use. Studies resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English were included.

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