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Glucodynamics and glucocracy in type 2 diabetes mellitus: clinical evidence and practice-based opinion on modern sulfonylurea use, from an International Expert Group (South Asia, Middle East & Africa) via modified Delphi method

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Glucodynamics and glucocracy in type 2 diabetes mellitus: clinical evidence and practice-based opinion on modern sulfonylurea use, from an International Expert Group (South Asia, Middle East & Africa) via modified Delphi method

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a global epidemic. According to international guidelines, the management protocol of T2DM includes lowering of blood glucose, along with preventing disease-related complications and maintaining optimal quality of life. Further, the guidelines recommend the use of a patient-centric approaches for the management of T2DM; however, Asian population is underrepresented in landmark cardiovascular outcome trials (CVOTs). There are several guidelines available today for the diagnosis and management of T2DM, and hence there is much confusion among practitioners about which guidelines to follow. A group of thirty international clinical experts comprising of endocrinologists, diabetologists and cardiologist from South Asia, Middle East and Africa met at New Delhi, India on February 8 and 9, 2020 and developed an international expert opinion statements *via* a structured modified Delphi method on the glucodynamic properties of OADs and the glucocratic treatment approach for the management of T2DM. In this modified Delphi consensus report, we document the glucodynamic properties of Modern SUs in terms of glucoconfidence, glucosafety, and gluconomics. According to glucodynamics theory, an ideal antidiabetic drug should be efficacious, safe, and affordable. Modern SUs as a class of OADs that have demonstrated optimal glucodynamics in terms of glucoconfidence, glucosafety, and gluconomics. Hence, modern SUs are most suitable second line drug after metformin for developing countries. Based on the current evidence, we recommend a glucocratic approach for the treatment of T2DM, where an individualized treatment plan with phenotype, lifestyle, environmental, social, and cultural factors should be considered for persons with T2DM in the South Asian, Middle Eastern and African regions.

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Introduction

Diabetes mellitus (DM) is a global epidemic with an estimated worldwide prevalence of 463 million in 2019, a figure projected to reach 578 million by 2030 and 700 million by 2040[1]. The increasing prevalence of DM is attributed to a variety of factors, including the rise in the aging population, ethnicity, change in lifestyle, obesity, socioeconomic status, and urbanization[2]. The increasing prevalence in DM is associated with a significant increase in complications like cardiovascular diseases, end-stage renal disease, neuropathy, and retinopathy[3].

According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the therapeutic goals of type 2 diabetes mellitus (T2DM) include prevention/delaying of complications and maintaining the quality of life. To achieve these therapeutic goals, the international guidelines recommend control of blood glucose along with cardiovascular risk factor management, regular follow-up, and the adoption of a patient-centered approach[4]. The most appropriate approach for the management of T2DM includes an initial evaluation of the patient's risk factors—including diabetic complications, along with reviewing any previous treatments. This will ensure the optimal management of diabetes[5]. Effective managements of T2DM entails lifestyle modification, as well as pharmacologic therapies, to ensure individualized glycemic control.

Oral antidiabetic (OAD) therapy along with lifestyle modifications is the initial line of therapy for T2DM. Factors that are considered while prescribing an OAD include safety, efficacy, tolerability, and cost-effectiveness[6]. Sulfonylureas (SUs) are one of the oldest and most important class of OADs that are currently available for the management of T2DM. Modern SUs (glimepiride and gliclazide MR) are more effective and have a better safety profile as compared to conventional SUs (glibenclamide) and are also associated with additional pleiotropic benefits, such as anti-inflammatory and immunomodulatory effects, along with endocrine and metabolic effects[6].

Recent international guidelines recommend, a glucose-lowering medication with proven cardiovascular and/or mortality-reducing benefit for patients with T2DM in whom lifestyle modification and metformin use have failed to achieve glycemic targets[7]. Guidelines should consider lifestyle, phenotype, social and cultural factors—along with patient preferences and comorbidities. In this context, an initiative by an international task force of experts aimed to highlight the glucodynamic properties of the oldest prescribed antidiabetic drug class, viz. SUs, and to describe the glucocratic approach for the treatment of T2DM. This international expert opinion aims to update the clinicians by providing multi-disciplinary guidance for the management of T2DM.

Methodology

During a two-day international task force meeting (Safe & Smart) on February 8 and 92,020 at New Delhi, India, thirty experts from South Asian, Middle Eastern and African reviewed available literature evidence and provided individual insights based on experience for the management of DM. The primary focus was on the glucodynamic and glucocratic benefits of OADs with a focus on modern SUs. The experts then formulated key opinions based on scientific evidence and clinical judgment. Clinical expert opinions issued for each topic are summarized in this article.

The modified Delphi method was chosen for arriving at an expert opinion consensus with all the experts. The Delphi method originated in the 1950s and Delphi takes its name from the oracle of Delphi – a tribute to the skills of interpretation and foresight[8]. This method was developed at the RAND Corporation and was found to be a reliable consensus of opinion of a group of experts on a subject in a systematic manner. This is generally applied when consensus among a large number of participants is needed[9].

The Delphi technique obtains consensus from an expert group through a series of well-defined questionnaires, based on surveys and feedbacks. The Delphi method is a consensus-based technique wherein a systematic approach is employed for collecting and aggregating informed judgments from a group of experts. The detailed steps involved in the Delphi process are outlined in Figure 1. In the present expert meeting, the survey questions were voted upon and the results presented before each session. For questions for which consensus was not achieved ($<$80%), re-voting was carried out after presenting the available evidence. The present article describes the opinions of the experts and their recommendations for items that obtained $\geq$80% consensus.

Glucodynamics of modern SUs

Glucodynamics is a holistic therapeutic approach for DM management, wherein the emphasis is to take care and control blood glucose levels along with associated vascular and metabolic conditions in order to optimize the efficacy and minimize the side effects of treatment. This approach considers the efficacy, safety, and economic factors of DM treatment.

Glucodynamics considers three parameters, viz. glucoconfidence, glucosafety, and gluconomics.

1. Glucoconfidence refers to reliability of glycemic control and management of individuals with type 2 diabetes mellitus (T2DM).
2. Glucosafety refers to the safety and tolerability of glucose-lowering drugs in both the short-term and long-term. Glucosafety also conveys the concept of cardiovascular safety.
3. Gluconomics plays an important role in the management of T2DM. In developing countries, the cost of diabetes therapy is largely out-of-pocket expense and contributes to catastrophic healthcare expenditure

Glucoconfidence refers to the efficacy of the OADs in achieving glycemic control and controlling other complications. The meta-analysis study by Hirst et al. describes the

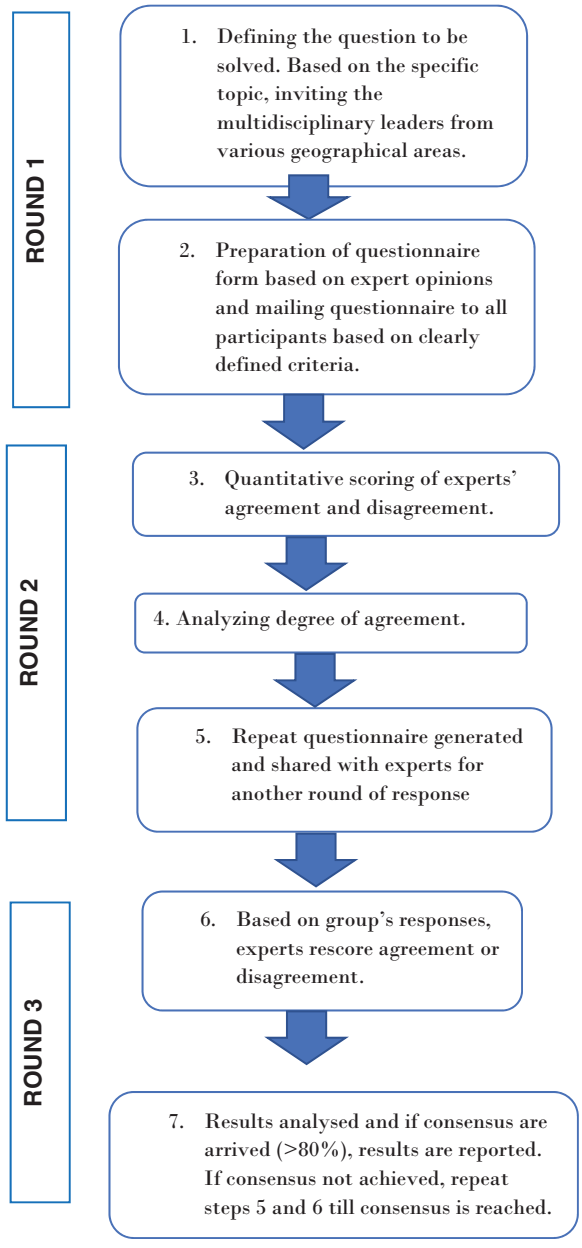

Figure 1. Flow chart depicting the modified Delphi technique.

glucose-controlling effect of SUs in T2DM. According to this study, which included 31 trials, the reduction in glycated haemoglobin (HbA_{1c}) with SU monotherapy was 1.51% (17 mmol/mol) higher than achieved with placebo (95% confidence interval [CI], 1.25, 1.78), while the reduction in HbA_{1c} with SU combination therapy (along with other OADs) was 1.62% (18 mmol/mol; 95% CI 1.0, 2.24) higher than that attained with other treatments. It was also observed that SU added to insulin lowered HbA_{1c} by 0.46% (6 mmol/mol; 95% CI 0.24, 0.69), thereby further lowering the insulin dose[10]. The randomized controlled trial (RCT) by Kudaravalli et al. describes the glycemic control achieved with glimepiride compared to placebo and glipizide. In this study, which involved 100 diabetic patients and 24 healthy controls, preprandial blood glucose levels were significantly lower after glimepiride therapy compared to placebo and glipizide. Further, postprandial blood glucose was significantly higher after glipizide therapy compared to glimepiride therapy, with both glimepiride and glipizide having similar effects on insulin secretion[11]. The Indian multicentric START study also reported the clinical benefits of glimepiride in combination with metformin compared to sitagliptin with metformin. According to the START study, there was a statistically more significant reduction in the mean HbA_{1c} in the glimepiride group compared to the sitagliptin group (0.42 vs. 0.30%, $p = .001$). Further, there was also a more significant reduction in fasting plasma glucose and postprandial glucose in the glimepiride group compared to the sitagliptin group ($p = .008$)[12]. The RCTs by Nauck et al. and the ADVANCE collaborative group have reported the efficacy of modern SUs along with other OADs in terms of reducing glycated hemoglobin and the incidence of combined major macrovascular and microvascular events[13,14].

Further, it is also reported that modern SUs when added to insulin therapy increase endogenous insulin secretion, thereby exerting extra pancreatic effects on certain tissues, which in turn improve glycemic control and reduce daily insulin requirements[15].

Glucosafety refers to the safety profile of modern SUs achieved by reducing the risk of drug-related complications. Although SUs are generally well-tolerated, weight gain and hypoglycemia are commonly reported adverse events with SUs along with questionable long-term cardiovascular (CV) safety[16]. Hypoglycemia is one of the important clinical concerns associated with the use of SUs; it is more common with long-acting sulfonylureas such as chlorpropamide and glibenclamide[17]. The experts opined that the incidence of hypoglycemia is relatively lower with modern SUs. The GUIDE study by Schernthaner et al., conducted to evaluate the efficacy and safety of two modern SUs (gliclazide and glimepiride), reported hypoglycemia in 66 and 69% of patients treated with gliclazide and glimepiride respectively. Further, there were no episodes of hypoglycemia that required external assistance or nocturnal symptomatic episodes[18]. The study by Devarajan et al. also reported a comparable incidence of hypoglycemia in patients treated with glimepiride and sitagliptin[12]. The meta-analysis conducted by Landman et al. reported lower rates of severe hypoglycemia with gliclazide compared to other antidiabetic drugs[19]. However, the RCT by Vaccaro et al. reported significantly lesser hypoglycemia in the pioglitazone group compared to the SU group (10 vs 34%, $p < .0001$)[20]. Similar results have been reported in the Korean multicentric open-label, parallel-group study by Kim et al. wherein the incidence of hypoglycemia was significantly higher with glimepiride/metformin fixed-dose combination compared to metformin up-titration (41 vs. 5.6%, $p < .0001$); however, there was no serious hypoglycemia in any group[21]. Further the meta-analysis by Zhang et al. also reported a lower risk of hypoglycemia with DPP-4 inhibitors compared to SUs (MH-OR, 0.13; 95% CI 0.11–0.16)[22]. Hence the experts opined that it is important to caution people with diabetes about the circumstances in which hypoglycemia may occur, especially after a missed meal or after exercise or when taking an excessive dosage. Further, experts

also opined that by starting the therapy with low-dose SUs may help manage hypoglycemia.

The other common side effect of SUs is weight gain, which is also reported with insulin, thiazolidinediones, and glinides. In the UKPDS study, patients treated with SU monotherapy gained more weight compared to dietary intervention, with 2.6 kg weight gain noted in the chlorpropamide group and 1.7 kg weight gain noted in the glibenclamide group[23]. However, meta-analysis shows glimepiride have weight-neutral effects in patients with T2DM[24,25]. Further, the GUIDE study also reported stable body weight, with mean changes of 83.1–83.6 kg and 83.7–84.3 kg with gliclazide MR and glimepiride, respectively[18]. The follow-up study by Weitgasser et al. reported significant, stable weight loss following treatment with glimepiride (mean reduction reported: 79.8 kg at baseline to 77.9 kg after 4 months, $p < .0001$; 77.2 kg after 1 year, $p < .05$ and 76.9 kg after 1.5 years, $p < .005$). Based on the results of the study, the investigators reported that once-daily glimepiride is associated with a weight-neutralizing effect in patients with T2DM[26]. Similarly, the double-blind randomized STEADFAST study demonstrated similar weight reduction in patients treated with SU and vildagliptin (-1.1 ± 0.2 kg, $p = .987$)[27].

According to the recent ADA guidelines, cardiovascular risk factors should be assessed annually for all diabetic patients[28]. The controversies over the cardiovascular safety of SUs were raised because of the results of the University Group Diabetes Program (UGDP) study, wherein the investigators reported an increased association between tolbutamide use and the risk of coronary artery events[29]. However, the UGDP study had many flaws in terms of study design and statistical techniques. Further studies evaluating the safety and efficacy of SUs have not reported such concerns. Of note, modern SUs (glimepiride & gliclazide MR) are associated with fewer cardiovascular events compared to other SUs[25]. According to the case-control study by Sadikot and Mogensen, the risk of coronary artery disease increased by 2.4-fold (1.3–4.3, $p = .004$) with glibenclamide and 2-fold (0.9–4.6, $p = .099$) with glipizide, while the hazard decreased 0.3-fold (0.7–1.7, $p = .385$) with glimepiride and 0.4-fold (0.7–1.3, $p = .192$) with gliclazide[30]. Further, the results of the recent Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) demonstrated no difference in the composite of time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke between the linagliptin and glimepiride groups[16].

Gluconomics refers to reducing the economic burden of treatment. According to a prospective epidemiological study by Chow et al., the availability and affordability of essential medications for diabetes management are poor in a few low-income countries[31]. The estimated total annual costs for diabetes care in South Asia range from $483 to $2637 per patient. It is further reported that 5.8% of patients with diabetes reduce their basic expenditure by 40% to manage the treatment burden because of a lack of a proper insurance system[32]. Hence it is very important to consider the cost of treatment while prescribing any drug, especially in developing countries. A study by Klarenbach et al. reported the cost-effectiveness of SUs. In this study, the addition of a SU to metformin was associated with the lowest total lifetime costs ($40,669), while the addition of biphasic insulin had the highest lifetime costs ($52,367). Further, the combination of SUs and metformin was associated with more favorable cost-effectiveness estimates (incremental cost of $12,757 per quality-adjusted life-year) compared to metformin monotherapy[33]. The study by Zhang et al. also reported SUs to be significantly associated with a lower cost per quality-adjusted life-years (QALY), as well as the longest time of insulin independence, compared to all other regimens[34]. Previously, SU-induced hypoglycemic events were reported to increase the cost of treatment; however, these have been mitigated with the use of modern or newer SUs[35].

Based on available evidence from literature and the consensus agreement, the expert panel put forward the glucodynamic approach for DM management, focusing on modern SUs (Box 1).

The numbers in parentheses represent % of experts who agreed with the particular statement.

Box 1. Modified Delphi consensus on Glucodynamics of sulfonylureas along with percentage of consensus.

- A holistic therapeutic approach works best for the management of people with type 2 diabetes in our region (100%).
- The ideal component of the holistic therapeutic approach includes the efficacy (glucoconfidence), safety (glucosafety), and economic burden (gluconomics) (100%).
- The judicious use of modern sulfonylureas (SUs) can minimize hypoglycemia (95.5%).
- Weight gain is not major concerns with modern SUs compared with conventional SUs (81.8%)
- A cost-effective approach involving the use of easily available and affordable antidiabetic medications for the management of type 2 diabetes mellitus (T2DM) is crucial as recommended by the World Health Organization (100%).
- The extra pancreatic and pleiotropic effects of modern SUs help in positioning them as oral antidiabetics (OADs) of choice after Metformin (86.9%).
- Simple clinical characteristics, such as body mass index (BMI), age at diagnosis, and duration of diabetes, help to identify differences in glycemic response and highlight the side effects of SUs (87.5%).
- If HbA_{1c} is >7.5% at diagnosis, a modern SU can be added to the treatment regimen for effective and rapid glycemic control (86.4%).
- The use of Modern SUs in combination with basal insulin can decrease the dose of basal insulin, ensure a good glycemic effect without up titration of insulins (92%).

Box 2. Modified Delphi consensus on Glucocratic approach in the treatment of T2DM along with percentage of consensus.

- Most subjects with T2DM treated in primary care settings do not have similar characteristics as the subjects enrolled in international CVOTs (91%).
- The T2DM management guidelines should be more region-specific, as there is vast diversity in the phenotype, lifestyle, environmental, social, and cultural factors across different regions of the world (91%).
- Modern SUs could be considered potential drug for the glucocratic OAD charter in South Asia, the Middle East, and Africa. SUs are included in the national list of essential medicines in most countries in these regions (100%).
- Guidelines uniformly recommend metformin as a first line OAD for managing diabetes (95.65%).
- Swift blood glucose control, CV protection, renal protection, durability, and tolerability are the main factors that influence the choice of OAD (88%).
- Considering compliance and convenience, a fixed-dose combination of metformin and a modern SU is a preferred choice in South Asia, the Middle East, and Africa. (100%).

Glucocratic approach in treatment of T2DM

Glucocratic approach is a proposed democracy in therapeutic approach wherein the choice of OADs is based on the patients' glucophenotype, including severity of hyperglycemia and risk of hypoglycemia, along with their medical and vascular phenotype, lifestyle and socioenvironmental factors.

There is significant inconsistency in the current international guidelines for diabetes management. The recommendations have changed drastically over the past few years, and now propose newer drugs such as SGLT2 inhibitors for the first-line therapy of T2DM. As these guidelines are based on the results of studies conducted among specific diabetes populations, they may not be extrapolated to all populations and will not be cost effective for developing countries[28].

Further, the diversity of phenotypes, lifestyles, environmental, social, and cultural factors across different global regions prompts the need for developing a treatment approach specific to the region. In this scenario, a glucocratic approach would be highly beneficial.

Several cardiovascular outcome trials (CVOTs) have been conducted to address the cardiovascular side effects of antidiabetic therapies. The newer classes of antidiabetic drugs that have shown significant improvement in terms of cardiovascular protection include dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and sodium/glucose co-transporter-2 inhibitors (SGLT-2i)[36]. However, there was a huge ethnic discrepancy in terms of patient enrollment. Although T2DM is more common in the Asian population, only 13 to 21% of enrolled patients in these CVOTs were of Asian origin[37]. Further, these CVOTs had highly specific inclusion criteria, and hence the results cannot be extended to the diabetic population as a whole. Again, the risk and incidence of cardiovascular disease are different in the Asian and Western populations: Asians have a higher risk of stroke, while the Western population has an increased risk of coronary artery disease[38]. Hence, the application of the results to a larger group requires evidence from real-world studies conducted among different patient populations[39].

Furthermore, the global DISCOVER study was conducted to assess management strategies worldwide. According to this study, there are differences in the baseline characteristics of patients with T2DM. From the results of the DISCOVER study, it was noted that the mean BMI was lowest in the Western Pacific region and highest in the European region. It was also reported that the proportion of patients receiving a combination of metformin and SU as first-line therapy was higher in Southeast Asia and the Eastern Mediterranean region (31.1 and 23.9%, respectively). For second-line treatment, metformin along with SU was the most commonly prescribed treatment in the African (57.1%) and Southeast Asian (24.8%) populations, while a combination of metformin and DPP-4 inhibitors was the most commonly prescribed treatment in the Eastern Mediterranean region (29.6%), America (29.2%), Europe (27.5%), and the Western Pacific region (24.8%)[40].

It is important to develop regional guidelines for T2DM management, as this helps in upgrading currently available management strategies. It will also help healthcare providers to improve treatment while improving patients' quality of life[40]. Based on available evidence, the expert panel proposed the glucocratic approach for the management of T2DM, with a focus on modern SUs in the management algorithm (Box 2).

The numbers in parentheses represent % of experts who agreed with the particular statement.

Conclusion

Based on the evidence, the international task force opines modern SUs as a class of OADs that have demonstrated optimal glucodynamics in terms of glucoconfidence, glucosafety, and gluconomics. Hence modern SUs are most suitable second line drug after metformin for developing countries. Based on the current evidence, we recommend a glucocratic approach for the treatment of T2DM, where an individualized treatment plan with phenotype, lifestyle, environmental, social, and cultural factors should be considered while initiating OAD. A holistic treatment approach is therefore, mandatory and modern SUs meet the glucodynamic parameters in this regard.

Transparency

Declaration of funding

All authors had full access to the articles reviewed in this manuscript, have read and reviewed the final draft of this manuscript and take complete responsibility for the integrity and accuracy of this manuscript. The content published herein solely represents the views and opinions of the authors and does not necessarily represent the views or opinion of Sanofi and/or its affiliates. The details published herein are intended for informational, educational, academic and/or research purposes and are not intended to substitute for professional medical advice, diagnosis or treatment

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethical guidance

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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