Review Article

SULFONYLUREAS IN TYPE 2 DIABETES MELLITUS: CURRENT EVIDENCE, CONFLICTS AND CLINICAL IMPLICATIONS

Chiedozie Kenneth Ugwoke[1], Urban Slokar[2], Atsuhito Nakayama[3], Nejc Umek[4]

[1]Faculty of Medical Sciences, University of Nigeria, Nigeria
[2]General Hospital Dr. FrancDerganc, Nova Gorica, Slovenia
[3]Faculty of Medicine, The University of Tokyo, Japan
[4]General Hospital Novo Mesto, Slovenia

ABSTRACT

INTRODUCTION: We sought to explore the current state of evidence on sulfonylurea therapy in type 2 diabetes mellitus (T2DM) and critically examine the recommendations of major practice guidelines, and the overall ramifications of the issues thereof in current clinical practice.

METHOD: We searched PUBMED, MEDLINE and other databases, and selected, analysed and interpreted relevant original studies, reports and reviews on the subject.

RESULTS: A compelling body of literature exist on the sulfonylurea use in T2DM, with a remarkable number of studies illuminating substantial clinical issues associated with their use. Nevertheless, definitive evidence is still limited in terms of unequivocally clarifying some of the concerns. All major practice guidelines mirrored a historical trend of consistent endorsement of sulfonylureas as first or second line agents in T2DM management. However, based on re-evaluation of available evidence, some latest guidelines have reflected a significantly declined confidence in the traditional status accorded to sulfonylureas in T2DM management, conspicuously contrasting other existing guidelines.

CONCLUSION: The apparent inconsistencies and deficiencies in the available body of evidence and the conflicting recommendations in current guidelines have raised new questions and complicated clinical considerations, creating a novel dilemma in the clinical use of sulfonylureas.

KEYWORDS: Sulfonylurea; type 2 diabetes mellitus; evidence; guidelines; clinical practice.

NigerJMed2017: 68-75

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, insulin insensitivity, declining insulin production, and eventual pancreatic β-cell failure [(1)]. The disease prevalence has been increasing steadily over the past 30 years, rapidly approaching epidemic proportions in many countries across the world. It is predicted that the prevalence of T2DM in adults will rise futher in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years [(2)]. Studies examining data trends within Africa point to evidence of a dramatic increase in prevalence in both rural and urban settings, affecting both gender equally [(3)].

Corresponding Author: Dr Chiedozie Kenneth Ugwoke,
Faculty of Medical Sciences, University of Nigeria, Nigeria.
Email: ugwoke.chiedozie@gmail.com
Phone number: +2347033028524

Although the pathogenesis and long-term complications of T2DM are fairly well known, its prevention and treatment remain challenging, with only half of the patients achieving the recommended level of glycated haemoglobin (HbA1c) [(4)]. Studies have shown that there was significant reduction in the incidence of T2DM with a combination of maintaining healthy body mass index, high fibre – low saturated and trans-fats diet, regular exercise, abstinence from smoking and moderate consumption of alcohol, suggesting that majority of T2DM can be prevented by lifestyle modification [(5-8)].

No cure has yet been found for the disease; however, treatment options in addition to lifestyle modifications include various classes of oral glucose lowering agents. Since the commercial introduction of sulfonylureas in 1956, till 1995, sulfonylureas and metformin were the only oral glucose lowering agents. From 1995 all of the other oral glucose lowering agents were introduced: α-glucosidase inhibitors (AG-i) in 1995,

thiazolidinediones (TZD) in 1996, meglitinides (GLN) in 1997, GLP-1 receptor agonists (GLP1-RA) in 2005, amylin agonists in 2005, DPP-4 inhibitors (DPP-4i) in 2006, colesevelam approved for T2DM in 2008, quick-release bromocriptine approved for T2DM in 2009 and SGLT-2 inhibitors (SGLT-2i) in 2013 [9]. As pointed out above, sulfonylureas have been a cornerstone of T2DM pharmacotherapy for over 50 years; however, their status in T2DM management has become a recent focus of interest due to apparent inconsistencies in evidence and contrasting recommendations among current guidelines.

Pharmacology of sulfonylureas

While the sulfonylureas represent a rational and effective class of antihyperglycemic agents, interindividual variability exists in their pharmacodynamics, pharmacokinetics and adverse effects. In order to elucidate the genetic underpinnings of this response variability, many studies have sought to determine the influence of drug-metabolizing enzyme polymorphism on sulfonylurea pharmacokinetics. In addition, polymorphisms in sulfonylurea target genes and diabetes genes have recently been recognised as important determinants of sulfonylurea pharmacodynamics in T2DM patients[10-12].

The evolution of sulfonylureas resulted in what is currently referred to as the different generations of agents (Table 1). They all have the same mechanism of action; however the second generation of sulfonylureas have higher potency than the first-generation agents [12]. Sulfonylureas stimulate insulin release by binding to ATP-sensitive potassium channels on the surface of pancreatic β-cells. Structurally, K+ATP-channels are hetero-octameric protein complex composed of inward-rectifying potassium channels (Kir6.2) and sulfonylurea receptor (SUR1) with a stoichiometry of 4:4, which make up one KATP-channel complex (Figure 1) [12]. Binding of sulfonylurea to SUR1 results in closure of the K+-ion channel, which leads to increased concentration of intracelular potassium, depolarization of β-cell mambrane, and the subsequent opening of voltage-gated calcium channels. Influx of calcium stimulates the glucose-independent exocytosis of insulin-containing secretory granules into the circulation[13]. As insulin secretagogues, sulfonylureas are dependent on functioning β-cells and are therefore usually used early in the course of the disease process. Later in the progress of T2DM, efficacy of sulfonylureas may decline with increasing dysfunction of β-cells, and a need for a dosage increase or a switch to other therapy may be necessary [12].

Both in vivo and in vitro studies have demonstrated that sulfonylurea treatment may also inhibit glycogenolysis and gluconeogenesis and stimulate glycogenesis and glycolitic pathway by regulatingthephosphofructokinase-2/ fructose2,6-bisphosphatase and phosphoenolpyruvate carboxykinase [14,15]. Sulfonylureas appear to reduce glucagon and free fatty acid concentration in the plasma, which may further contribute to the insulin sensitivity [14]. Some agents in the class also increase glucose uptake in the muscles, not only by increasing GLUT4 and GLUT1 expression but also by stimulating glycogenesis and lipogenesis [16,17].

The principal site of sulfonlyurea metabolism is the liver. There it is extensively metabolised primarily by the cytochrome P450 2C9 isoencyme, which gives rise to a relatively short half-life of most sulfonylureas (up to 10 hours), except for chlorpropramide, which has a half life of 24-48 hours [18]. In terms of efficacy, on average, sulfonylureas lower HbA1c by 1-2% [19].

Complications and adverse effects associated with sulfonylureas

Despite its strong antidiabetic action, several adverse effects of sulfonylureas are reported. The most common and worrisome adverse effect of sulfonylureas, more likely to occur with the longer acting agents (Table 1), is hypoglycaemia[20].β-cells in the pancreatic islet are constitutively stimulated by sulfonylurea to secrete insulin regardless of the plasma glucose level, leading to hypoglycaemia due to excessive insulin production. In the case of patients with diabetes older than 60 years of age, hypoglycaemia is ranked as the second most common non-fatal complication[21]. Hypoglycaemic events frequently cause sudden loss of consciousness, which is followed by traumatic injuries upon falling. A significant relationship exists between hypoglycaemia and fall-related fractures in older patients[22]. Thus, sulfonylureas should be used with caution in patients with irregular eating habits, alcoholics, those on β-blocker therapy and elderly patients.

Another important problem associated with sulfonylureas is an increased risk of mortality and cardiovascular events compared to other antidiabetic agents. This relationship is investigated in a number of existing studies. For example, the all-cause mortality for metformin-monotherapy was revealed to be significantly lower than that for sulfonylurea-monotherapy in T2DM patients[23]. Similarly, when glycaemic control with metformin failed, DPP-4i(linagliptin) caused fewer cardiovascular events than sulfonylurea as a second-line treatment[24]. The association with adverse cardiovascular effects is

explained by two mechanisms. One mechanism is the interaction of sulfonylureaswith certain subtypes of sulfonylurea receptors expressed in the heart and vessels. Whereas the pancreatic β-cells express SUR1, the myocyte and the vascular smooth muscle cell express SUR2A and SUR2B. These receptors couple with ATP-sensitive K+ channels, and in the presence of sulfonylurea, they inhibit cardiac conduction and the function of ischemic conditioning, a physiological protection of the myocytes against hypoxia. The other mechanism of sulfonylurea stems from frequent hypoglycaemic episodes, which prolongs QT interval and increases the risk of sudden death [25].

The third major adverse effect noted in connection with sulfonylureas is ablation of pancreatic β-cells. From in vitro studies, several sulfonylureas are known to induce apoptosis of cultured β-cell lines through production of reactive oxygen species [26,27]. However, this relationship is not proven in the clinical settings: a continuous decrease in β-cell mass is expected as the history of diabetes elongates, and therefore, whether sulfonylurea accelerates this trend or not remains debatable. On the other hand, GLP-1RA, insulin secretagogues that glucose-dependently act and imitate the physiological secreting pattern, induce proliferation of β-cells in a phosphatidylinositol-dependent manner in vitro[28]. Although this probabale adverse effect of sulfonylurea is hard to evaluate clinically, from a β-cell-preserving point of view, precautionary clinical judgement may favour significant dose minimization, or possible substitution by other antidiabetic agents.

The last major complication is weight gain through accumulation of the visceral fat tissue. Insulin is an assimilating hormone that promotes storage of glucose and synthesis of fatty acids, leading to proliferation of the white adipose tissue. The UKPDS and other past clinical trials reported weight gain in the patients on glibenclamide treatment. Furthermore, adipocytokines secreted from the fat tissue increases insulin resistance, which hinders diabetic treatment and also raises the risk of dyslipidemia, hypertension, or eventually metabolic syndrome. To prevent the vicious cycle, a proper diet and a good amount of physical exercise are essential to lower the risk of weight gain as much as possible[29].

Other rarely described adverse effects include: cholestatic jaundice, haemolyticanaemia, thrombocytopenia, agranulocytosis; and with chlorpropramide, flushing and hyponatremia[20].

Current guideline inconsistencies and clinical controversy

As noted earlier, the sulfonylurea is one of the oldest classes of antihyperglycemic agents in the pharmacotherapy of T2DM. Accordingly, all major clinical practice guidelines have traditionally accorded it an important position in T2DM management. The American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) guideline recommends sulfonylureas as first line (if metformin is contraindicated or not tolerated), or second/third line agent after metformin, if glycaemic target is not attained by monotherapy[30]. Similarly, the guidelines and position statements of the International Diabetes Federation (IDF), the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), South Asian Federation of Endocrine Societies (SAFES), as well as national guidelines from Canada, Japan, China and South Africa all reflect a generally congruent position of sulfonylureas as first or second line agent in T2DM treatment[31-38]. However, these recommendations are in conspicuous contrast to the latest guidelines of the American College of Physicians and the American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE) [39,40].

In 2012, the ACP updated its clinical practice guidelines on oral pharmacologic management of T2DM, based on a systematic evaluation of published evidence (from 1966 to 2010) comparing efficacy and safety of pharmacologic treatments for T2DM[40]. Among other recommendations, the new ACP guideline, like other traditional guidelines highlighted above, proposes that physicians should prescribe metformin (unless contraindicated) as initial pharmacologic therapy when lifestyle modification measures fail to adequately improve hyperglycaemia. This is on account of its extensively proven efficacy, safety and low cost. However, if metformin monotherapy fails to sufficiently control hyperglycaemia, the ACP guideline recommends addition of a second agent, but fails to stratify the efficacy of other pharmacologic options to guide preference. This, according to the authors, is because although some evidence suggests that dual therapy regimens containing metformin appear to be more effective than any other combination option, or monotherapy, there is generally insufficient or unclear evidence based on long term outcome measures, to recommend one second agent over another. Most long term clinical trials compared different levels of glycaemic reduction rather than direct head-to-head comparison between agents used to attain the glycaemic targets, and evidence from newer studies with more specific comparison are still considered preliminary in terms of long term treatment outcomes and clinical event reduction profile[41,42]. Nevertheless, the guideline does state clearly that high-quality evidence show that combination therapies containing

sulfonylureas carry greater risk of adverse effects. It noted that the risk of severe hypoglycaemia with sulfonylureas significantly exceeds that of metformin or TZDs, and that the metformin-sulfonylurea dual therapy was associated with six times greater risk of hypoglycaemia compared to metformin-TZD combination. Although, not explicitly stated in the guideline, it is prudent and rational to infer from these statements by the ACP that sulfonylureas may not be the preferred second line option in pharmacologic management of T2DM, and should perhaps be considered a third or fourth line option. This inference is consistent with the latest AACE/ACE guidelines[39].

The 2016 AACE/ACE Comprehensive Diabetes Management Algorithm considers sulfonylureas neither as first choice monotherapy option, nor as preferred option for dual or triple therapy(39). In fact, the algorithm ranks SU lowest among all FDA approved classes of medications for T2DM in the suggested hierarchy of preference for monotherapy (metformin>GLP1-RA>SGLT-2i>DPP4i>AG-I >TZD>sulfonylureas/GLN), dual therapy (GLP1-RA>SGLT-2i>DPP4i>TZD>basal insulin>colesevelam>bromocriptine QR>AG-I >sulfonylureas/GLN) or triple therapy (GLP1-RA>SGLT-2i>TZD>basal insulin>DPP-4i>colesevelam>bromocriptine QR>AG-I >sulfonylureas/GLN). While the guideline notes that all other pharmacologic agents are generally associated with fewer adverse events, it warns that sulfonylureas, (as well as TZDs and basal insulin) should be used with caution as they possess higher adverse event profile (hypoglycaemia, weight gain, renal and cardiovascular complications, etc.)[43]. Up to 20% of patients on insulin secretagogues experience medication-induced hypoglycaemia with sulfonylureas having the highest risk of severe hypoglycaemia of any noninsulin therapy [44]. Meanwhile, sulfonylurea-induced severe hypoglycaemia is more likely to be protracted with greater mortality compared to that induced by insulin[45]. Although sulfonylureas have notable glycaemic lowering benefit, it has been shown however, that focusing primarily on attaining optimal glycaemic limits (HbA1c$\leq$6.5%) increases the risk of serious hypoglycaemia without significant reduction in clinical complications[46]. While it considers that individual patient context or characteristics and medication properties should guide therapeutic agent selection, the AACE/ACE guideline emphasizes that minimizing the risk of hypoglycaemia and weight gain should be a treatment priority as a matter of safety, adherence and cost. Accordingly, since sulfonylureas are conspicuous culprits of these adverse events, they are consequently not considered very favourable options.

Moreover, while sulfonylureas have the beneficial reputation of low cost, the guideline notes that safety and efficacy should be given higher priority over initial acquisition cost of drugs, since medication cost is only a small fraction of the total cost of diabetic care, which includes monitoring requirements, risks of hypoglycaemia and weight gain, etc. [39]. In the Cost of Type 2 Diabetes in Europe Study, antidiabetic medications including insulin accounted for only about 7% of healthcare costs, compared to disease and management related hospitalizations, which accounted for 55% of total healthcare expenditure [47]. Furthermore, while sulfonylureas are known to have relatively potent HbA1c lowering effect, they are equally known to lack durability. In the ADOPT trial which compared the glycaemic durability of the sulfonylurea glyburide versus metformin versus rosiglitazone monotherapy, glycaemic efficacy in terms of reduction in fasting plasma glucose and HbA1c levels was greatest with glyburide at 6 months. Conversely however, long term glycaemic efficacy was worst with glyburide with a five-year treatment failure outcome of 34% as against 21% and 15% for metformin and rosiglitazone respectively [48]. A similar observation of secondary failure of glycaemic control with glibenclamide was also noted in the UKPDS trials. The AACE/ACE guideline notes that their lack of durability significantly limits the strength of recommendation of sulfonylureas.

Although a number of studies and meta-analyses have reported a substantially higher risk of mortality and cardiovascular complications with sulfonylureas compared to other antidiabetic agents [50,51], the SAFES consensus statement however, argues that many of the clinical concerns associated with sulfonylureas are agent-specific and should not be generalized for the drug class [34]. Accordingly, it recommends that modern sulfonylureas such as gliclazide and glimepiride should be preferred over conventional ones such as glibenclamide, especially in patients with increased risk of hypoglycaemia or cardiovascular disease, or those who are overweight or obese. For instance, different sulfonylurea agents vary in their hypoglycaemic potential, with gliclazide and glimepiride showing lower rates of hypoglycaemia compared to glibenclamide [52]. Similarly, a systematic review of three randomized control trials concluded that gliclazide was associated with the least incidence of secondary glycaemic failure from β-cell exhaustion, compared to glibenclamide and glipizide [53]. In addition, glimepiride and modified release gliclazide have been associated with weight neutrality, at least in the first year, and a five-year follow-up of the ADVANCE Trial reported similar weight neutrality in patients taking regimens containing gliclazide[54,55].

Gliclazide and glimepiride are also backed by favourable data in terms of reduction in all-cause mortality and better cardiovascular outcome, compared to glibenclamide and glipizide[25,50]. In the light of these specific agent-differences, it may be reasonable to suspect that the inconsistencies in guidelines in different practice landscapes may to some extent reflect the variations in the availability and prevalence of use of specific sulfonylurea agents in these jurisdictions.

Nevertheless, clinical concerns have heightened regarding the status of sulfonylureas in T2DM management especially in view of the significant discordances in the existing body of relevant literature and the latest guidelines. Overall, there is no clear consensus in practice, on whether sulfonylureas should be used initially, or when it should be added subsequent to an initial agent. There is also debate on the preference of specific agents within the class in different clinical situations, as well as their comparative safety, efficacy and pathophysiologic effects across different subgroups of T2DM patients, such as the newly diagnosed, the long standing patients, the obese, the elderly, the pregnant or lactating, the paediatric, the co-morbid, etc. It is also debatable which management approach is backed by superior evidence: a preferred order or algorithm of medications such as proposed by the AACE / ACE[39], or just leaving the decision to the variable interpretations and clinical judgements of individual physicians as suggested by the ADA / EASD [30]. Moreover, since most of the guidelines focus primarily on drug efficacy and safety elements, with less attention on the heterogeneous pathogenicity of the disease, the complex pathophysiologic basis and dynamic contexts of treatment, it is also not clear to what extent this limitation impacts on their clinical legitimacy. Furthermore, although treatment guidelines are not intended in principle to represent a rigid or absolute prescriptive template, they are nonetheless generally presumed to represent the highest authoritative articulation of evidence-informed recommendations of best practice. Unfortunately, a recent critical evaluation of major practice guidelines on oral antihyperglycemic drugs has however, revealed substantial variability in the guideline development process and significant inconsistencies of recommendations with available evidence [57], leaving further questions on the technical integrity and practical validity of existing guideline prescriptions.

Implications for current practice and perspectives on the way forward

While a remarkable body of literature exists on sulfonylurea use in T2DM, rigorous evidence is still limited in terms of clarifying the various issues noted in connection with their clinical application. Even though emphasis has recently shifted from group characterization to agent-specific judgement of the merits and demerits of sulfonylureas, there are still insufficient standard trials comprehensively evaluating the relative safety and efficacy of different sulfonylurea agents. Hence, overall, the current debate on the place of sulfonylureas, and the consequent clinical dilemma of its use in T2DM management is likely to continue, until more scrupulous evidence emerge to categorically define its status. Although a number of current guidelines do not favour their clinical preference, their risk-benefit advantage has yet to be completely debunked, and in many regions, they are still the most widely prescribed second line agents. Meanwhile, over the past two decades, many new oral glucose lowering agents with less short term side effects have expanded the therapeutic options. However, in addition to being comparatively more expensive, their long term safety and efficacy ramifications are still unknown.

The primary goal of management of T2DM remains to reduce the risk of macrovascular and microvascular complications, improve quality of life and prolong life expectancy of the patients. In meeting this goal, it is important to realize that the background medical history, the stage of diabetes, and the purpose of treatment are all different among the broad spectrum of diabetic patients, and that the best treatment strategy for each patient would sometimes violate the recommendations in guidelines. Accordingly, treatment targets such as definition of optimal glycemic indices should be individualized and dynamic, reflecting each patient's unique and evolving clinical circumstances and therapeutic requirements. So when considering the appropriate agent for a specific patient, many factors such as age, comorbidities, stage of disease, drug cost and patient's preferences need to be taken into account. Which factors would have greater influence in a physician's judgment would depend on each country's economic status, drug availability and national guidelines for T2DM treatment. In view of the clinical issues and concerns arising from the current sulfonylurea debate, this patient centred approach appears to be the most realistic concept for T2DM management in the current dispensation, and both physician and patient empowerment are imperative in this regard to ensure optimal treatment outcome.

Conflict of interest

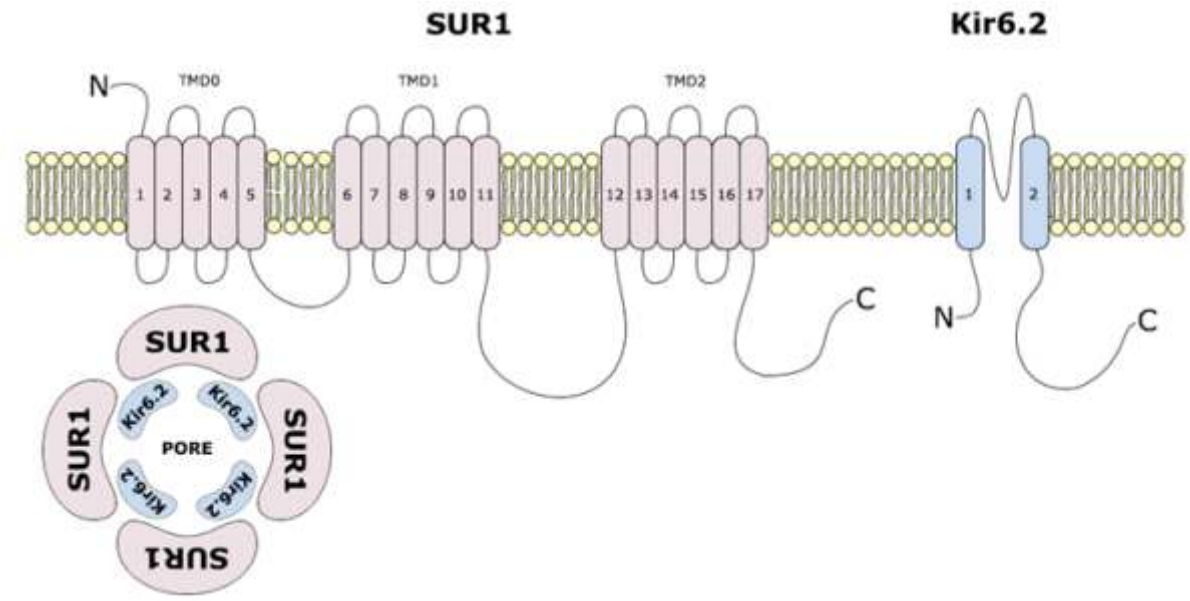
The authors confirm that this article content has no conflict of interest.

Table: Generations of sulfonylurea agents.

Sulfonylureas	*Short/intermediate acting*	*Long acting*
1. generation	tolazamide, tolbutamide, acetonexamide	chloropropramide, metahexamide
2. generation	glipizide, gliclazide, gliquidone	glybenclamide
(3. generation)		(glimepiride)

*Approximate location in the text indicated in the subsection 'Pharmacology of Sulfonylureas'

Figure : Schematic representation of the ATP-sensitive potassium channel complex.



*Approximate location in the text indicated in the subsection 'Pharmacology of Sulfonylureas'

REFERENCES

1. Kahn CR. Banting Lecture. Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes. 1994; 43(8): 1066-84.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimate for the year 2000 and projections for 2030. Diabetes Care. 2004; 127(5): 1047-53.
3. Mbanya JC. The Burden of Type 2 DM in the African Diaspora. [Online].; 2007 [cited 2016. Available from: "http://www.medscape.com/viewarticle/560718_2".
4. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism. 2011; 60(1): 1-23.
5. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nat Rev Endocrinol. 2011; 8(4): 228-36.
6. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007; 298(22): 2654-64.
7. Boffetta P, Mclerran D, Chan Y, et al. Body mass index and diabetes mellitus in Asia. A cross sectional pooled analysis of 900,000 individuals in the Asia cohort consortium 2011. PLoS One. 2011; 6(6): p. e19930.
8. Chiniwala N, Jabbour S. Management of diabetes mellitus in the elderly. Curr Opin Endocrinol Diabetes Obes. 2011; 18(2): 148-52.
9. White JRJ. A Brief History of the Development of Diabetes Medications. Diabetes Spectr. 2014; 27(2): 82-6.

10. Kirchheiner J, Roots I, Goldammer M, Rosenkranz B, Brockmoller J. Effect of genetic polymorphisms in cytochrome p450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. Clin. Pharmacokinet. 2005; 44(12): 1209–25.
11. Pacanowski MA, Hopley CW, Aquilante CL. Interindividual variability in oral antidiabetic drug disposition and response: the role of drug transporter polymorphisms. Expert Opin Drug Metab Toxicol. 2008; 4(5): 529-44.
12. Aquilante CL. Sulfonylurea pharmacogenomics in type 2 diabetes: The influence of drug target and diabetes risk polymorphisms. Expert Rev Cardiovasc Ther. 2010; 8(3): 359-72.
13. Reis AF, Velho G. Sulfonylurea receptor -1 (SUR1): genetic and metabolic evidences for a role in the susceptibility to type 2 diabetes mellitus. Diabetes Metab. 2002; 28(1): 14-9.
14. Del Prato S, Vigili de Kreutzenberg S, Riccio A, Tiengo A. Hepatic sensitivity to insulin: Effects of sulfonylurea drugs. Am J Med. 1991; 90(6): S29–S36.
15. Kaku K, Inoue Y, Kaneko T. Extrapancreatic effects of sulfonylurea drugs. Diabetes Res Clin Pract. 1995;: Suppl:S105-8.
16. Imamur H, Morimoto I, Tanaka Y, et al. Regulation of glucose transporter 1 expression by gliclazide in rat L6. Diabetes Nutr Metab. 2001; 14(6): 308-14.
17. Haupt A, Kausch C, Dahl D, et al. Effect of glimepiride on insulin-stimulated glycogen synthesis in cultured human skeletal muscle cells: a comparison to glibenclamide. Diabetes Care. 2002; 25(12): 2129–32.
18. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents. An update. Clin Pharmacokinet. 1989; 16(2): 100-28.
19. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care. 2009; 32(1): 193–203.
20. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs. 2005; 65(3): 385-411.
21. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med. 2014; 174: 251-8.
22. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012; 14: 634-43.
23. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care. 2002; 25: 2244-8.
24. Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012; 380(6840): 475-83.
25. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Feathersone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. Lancet Diabetes Endocrinol. 2015; 3: 43-51.
26. Maedler K, Carr RD, Bosco D, Zuellig RA, Berney T, Donath MY. Sulfonylurea induced beta-cell apoptosis in cultured human islets. J Clin Endocrionl Metab. 2005; 90: 501-6.
27. Sawada F, Inoguchi T, Tsobouchi H, et al. Differential effect of sulfonylureas on production of reactive oxygen species and apoptosis in cultured pancreatic beta-cell line, MIN6. Metabolism. 2008; 57(8): 1038-45.
28. Buteau J, Foisy S, Joly E, Prentki M. Glucagon-like peptide 1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes. 2003; 52: 124-32.
29. Hollander P. Anti-Diabetes and Anti-Obesity Medications: Effects on Weight in People With Diabetes. Diabetes Spectrum. 2007; 20: 159-65.
30. Inzucchi SE, Bergenstal MR, Buse BJ, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015; 58: 429-442.
31. Force ICGT. Global Guideline for Type 2 Diabetes. [Online].; 2012 [cited 2016 November 19. Available from: "http://www.idf.org/guideline-type-2-diabetes".
32. Guidance NIfHaCE. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). National Collaborating Centre for Chronic Conditions (UK). 2009.
33. SIGN. Management of diabetes. (SIGN Guideline No 116). [Online].; 2010 [cited 2016 November 19. Available from: "www.sign.ac.uk/pdf/sign116.pdf".
34. Kalra S, Aamir AH, Raza A, et al. Place of

sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015; 19(5): 577-96.
35. Haper W, Clement M, Goldenberg R, et al. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2013; 37: S61-S68.
36. Society JD. Treatement Guide for diabetes 2014-2015. [Online].; 2015 [cited 2016 November 19. Available from: "www.fa.kyorin.co.jp/jds/uploads/Treatment_Guide_for_Diabetes_2014-2015.pdf".
37. Society CD. China Guideline for type 2 Diabetes. Chin J Diabetes. 2010; 2: 1-56.
38. Amod A, Ascott-Evans BH, Berg GI, Blom DJ, Brown SL, Carrihill MM. The 2012 SEMDSA guideline for the management of type 2 diabetes (revised). The 2012 SEMDSA treatment algorithm for type 2 diabetes. J Endocrinol Metab Diabetes S Afr. 2012; 17 Suppl 1: S36-40.
39. Garber AJ, Abrahamson MJ, Brazilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2016 Executive Summary. Endocr Pract. 2016; 22(1): 84-113.
40. Qaseem A, Humprey LL, Sweet DE, Starkey M, Shekelle P. Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012; 156(3): W-43.
41. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011; 343: doi: 10.1136.
42. Fang HJ, Zhou YH, Tian YJ, Du HY, Sun YX, Zhong LY. Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: A meta-analysis of data from 58,160 patients in 13 randomized controlled trials. Int J Cardiol. 2016; 218: 50-8.
43. Frost T, Hanefeld M, Jacob S, et al. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Diab Vasc Dis Res. 2013; 10(4): 302-14.
44. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. Diabetes Care. 1989; 12: 209-8.
45. Ferner RE, Neil HA. Sulphonylureas and hypoglycemia. BMJ. 1988; 296: 949-50.
46. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358(24): 2560-72.
47. Jonsson B. Revealing the cost of type II diabetes in Europe. Diabetologia. 2002; 45: S5-S12.
48. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006; 355(23): 2427-43.
49. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352(9131): 854-65.
50. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013; 15: 938-53.
51. Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med. 2013; 30: 1160-71.
52. Landman GW, de Bock GH, van Hateren KJ, et al. Safety and efficacy of gliclazide as treatment for type 2 diabetes: a systematic review and meta-analysis of randomized trials. PLoS One. 2014; 9(2): p. e82880.
53. Harrower AD. Comparison of efficacy, secondary failure rate, and complications of sulfonylureas. Diabetes Complications. 1994; 8: 201-3.
54. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest. 2004; 34(8): 535-42.
55. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl Med. 2014; 371(15): 1392-406.
56. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: A systematic review and network meta analysis. Lancet Diabetes Ndocrinol. 2015; 3: 43-51.
57. Bennett WL, Odelola OA, Wilson LM, et al. Evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus: a systematic review. Ann Intern Med. 2012; 156(1): 27-36.