Role of age and sex in the incidence of adverse effects among diabetic patients treated with glipizide

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Abstract. Glipizide is an antidiabetic drug that belongs to a class of medication known as sulfonylureas. It is considered one of the highly prescribed antidiabetic drugs for the treatment of type II diabetes in patients following a kidney transplant. It lowers blood glucose levels by causing the release of insulin from β-cells in the pancreas. Its main metabolizing pathway is through the liver. It has several adverse effects, which range from an upset stomach to glipizide-induced haemolytic anaemia and hypoglycaemia. These adverse effects may be spontaneous, or they could have a genetic cause. The present study aimed to assess and document the incidence of glipizide-induced adverse reactions among patients prescribed the drug. The present retrospective case-control study used the electronic medical records of patients prescribed glipizide for the past 3 years. These records were reviewed to extract and document cases and/or signs of glipizide-induced adverse reactions. The results revealed that the incidence of adverse effects was higher among female patients (odds ratio, 2.40, P<0.001). Moreover, the results revealed that the likelihood of developing adverse drug reactions among patients <40 years of age was higher than in older patients (P>0.05). The outcomes of the present study are expected to prompt future studies to take sex and age into consideration, in an aim to improve treatment outcomes, reduce adverse events and decrease the burden of unnecessary costs for healthcare systems. Recommendations also include genetic screening prior to administering the medication, educating the patients and caregivers on the possibility of adverse drug reactions, and routine follow-up. This issue is of utmost importance to achieve the optimal outcomes with the minimal detrimental effects.

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Introduction

Glipizide is an antidiabetic drug that belongs to a class of medications known as sulfonylureas. It is specifically a second-generation sulfonylurea and one of the numerous antidiabetic drugs found in the market. It is administered to patients with type 2 diabetes mellitus (T2DM) for the control of high blood sugar levels (1,2). Type 2 diabetes is a form of diabetes that is caused by a combination of behavioural and genetic factors. It is also a very common chronic metabolic disorder in which the patient would have insulin insensitivity (3). This insensitivity is due to insulin resistance in tissues, which leads to a decrease in the production of insulin. As a result, the β-cells in the islets of the pancreas eventually fail to produce insulin (3). Glipizide causes the β-cells in the pancreatic islets to produce, release and efficiently use insulin. It also decreases the output of glucose from the liver and increases the insulin sensitivity in the peripheral tissues (4,5). Its initial effect occurs at 30 min post-administration and lasts from 12 to 24 h (6).

The main mechanism of action glipizide is that it causes the closure of ATP-sensitive potassium channels (K_{ATP} channel) by binding to a receptor on the plasma membrane of pancreatic β-cells (7). The closure of the K_{ATP} channel reduces the conductance of potassium, which causes the β-cells to become depolarized. This depolarization in turn opens the voltage-sensitive calcium channels and calcium ions flow into the cell. When the intracellular calcium ion concentration increases, insulin granules are secreted from the β-cells (5). Glipizide also lowers blood glucose levels by increasing the utilization of peripheral glucose through the stimulation of hepatic gluconeogenesis, and increasing both the sensitivity and number of insulin receptors (8). Moreover, the fact that

glipizide is a second-generation sulfonylurea, sulfonylureas with a more non-polar side chain, provides it with the advantage of having a more potent hypoglycaemic effect. Since the main metabolizing pathway of glipizide is through the liver, it is eliminated by hepatic biotransformation. Its metabolites are mainly excreted in urine, reaching ~80% (5,9). The remaining 20% of the drug are divided further into 10% excreted in faeces and 10% unaltered glipizide detected in both urine and faeces (9).

Glipizide is generally a safe oral antidiabetic drug (5). However, as with all medications, glipizide has a list of adverse effects, which range from an upset stomach to some severe side-effects that may require hospitalization. Issues with the gastrointestinal tract, such as constipation, diarrhoea, loss of appetite, nausea and vomiting are considered common and are among the few side-effects which do not require medical intervention (5). However, some patients may experience more severe adverse effects, such as fever or sore throat, which could indicate an infection, weight or mood changes, bleeding, bruising, yellowing of the skin or eyes, notable darkening of the urine, or a persistent or severe allergic reaction. These symptoms require urgent management and may lead to the discontinuation of the medication (4,5).

The pharmacokinetics of several medications are highly influenced by the cytochrome P450 family genetic polymorphism (10). Even though sulfonylureas are preferred in some types of monogenic diabetes, treatment is still based on the genotype of the patients (11). Of note, two of the most serious adverse effects of glipizide are hypoglycaemia and haemolytic anaemia (5), both of which have been linked to the patient carrying certain genetic variants. The presence of genetic variants of several genes, including cytochrome P450 family 2 (CYP2)C9 or CYP2C19 isoenzymes, transcription factor 7-like 2 (TCF7L2), and potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) causes the patient to have glipizide-induced hypoglycaemia (11,12). Moreover, glucose-6-phosphate dehydrogenase (G6PD)-deficient patients have been shown to have a higher incidence of glipizide-induced haemolytic anaemia (5). Due to the increased prevalence of G6PD deficiency among several populations, G6PD deficiency screening in newborns takes place in certain non-western countries, including Eastern Europe, the Middle East and Southeast Asia (13). Moreover, G6PD deficiency is increasing in Canada due to the large number of immigrants that have joined the Canadian population, which led to a study calling to implement the screening of newborns in populations which are at risk (13).

Although the 'one size fits all' is the predominant concept in the medical world whether it is in research or clinical practice, it is far from true (14). Females and males differ in a number of ways, including how their bodies respond to certain drug treatments. Both pharmacokinetics and pharmacodynamics are causes for sex differences in the occurrence of adverse events. As the volume of distribution in a female is much less than that of a male, the free fraction of the drug is larger, and the clearance of the medication from the body is slower; thus, females tend to be more frequently overdosed. Females are also more sensitive due to certain pharmacological factors, such as receptor number and binding alteration and the alteration in the signal transduction following receptor binding (15). Moreover, T2DM alters the ionization of weak acids and bases in the gastroenteric tract, which affects the absorption of certain medications, including glipizide (14). In addition, patients on glipizide develop glycosuria, excess sugar levels in urine. Glycosuria occurs in particular in females >60 years of age (16). This excess sugar allows different microbial strains to grow, causing the patient to develop a urinary tract infection (UTI). (17) Since the urethra in females is shorter than that in males, UTIs occur more often in females (18).

Taking into consideration the fact that the sex, age and genetic build-up of patient play a major role in the effects of a drug in different patients, precision medicine needs to be implemented to yield the optimal outcome following the administration of glipizide with the minimal amount of adverse effects (14-16). Moreover, since consanguinity is very common among the gulf countries, genetic polymorphisms tend to occur more frequently, and the incidence of individuals carrying and passing on certain genetic mutations and variants is significantly higher (19). Therefore, due to the role that genetics play in the effects of glipizide on a patient, consanguinity must play a crucial role on how a patient will respond to glipizide. Thus, Saudi patients are expected to be at an increased risk of developing severe glipizide-induced adverse effects.

The present retrospective case control study aimed to take pharmacogenetics into consideration through screening for certain genetic factors that could significantly affect the pharmacokinetics and pharmacodynamics of a drug. Moreover, it is highly essential to consider the age and sex of a patient prior to prescribing glipizide. This issue is of utmost importance to allow physicians to anticipate if the patient is a good candidate, and to avoid any dire and life-threatening side-effects. This will also ensure that the patient will tolerate the medication in the optimal way possible for an improved outcome.

Patients and methods

Patient data. Anonymous data were retrospectively collected for patients from King Faisal Specialist Hospital and Research Centre (KFSH&RC) who received the glipizide prescription between January, 2018 and December, 2020. Patient demographic and medication related data were collected, including age, sex, dose used and medication duration (months). Data on adverse drug reactions (ADRs) were also collected, including hypoglycaemia and haemolytic anaemia, as well as other common ADRs, including drug-induced fever, unspecified fever, nausea and vomiting, abnormal weight loss, throat pain, unspecified abnormal urine finding, specified disease of the stomach and duodenum, unspecified mood (affective) disorder, specified abnormal uterine and vaginal bleeding, asthma, and skin and subcutaneous haemangiomas. Data were processed in accordance with the best practices for raw data management to identify any inaccuracies or incompleteness before the statistical analyses. Data items were examined and compared against the possible minimum and maximum values of each variable and items with implausible values were flagged. A similar process was applied to demographic variables to identify any potential anomalies by running general frequency analyses.

The present study was approved by the office of Research Affairs of King Faisal Specialist Hospital and Research

Centre on the November 5, 2021 under the approval no. RAC# 2211211 and manuscript approval no. 2235443. The requirement for patient consent was waived by the committee due to retrospective nature of the study.

Statistical analysis. Statistical analyses were performed on the study population. All statistical analyses were performed using IBM SPSS 29.0 software (IBM Corp.). Continuous variables are presented as the mean and standard deviation (SD), median and IQR; and proportions were used for nominal and ordinal variables. The rate of ADRs was evaluated overall, and by demographic and medication related factors. Comparisons were made using the Chi-squared test. A logistic regression model was utilized to examine the independent effect of demographic and medication-related data on the rate of ADRs. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 830 patients were included. The data on demographic and drug-related factors of the patients are presented in Table I. The average age of the patients was 61.4 years (SD, 13.9 years), with 57.1% of the study population being males. The average duration of medication was 25.7 months (SD, 19 months); 77% of the patients used the drug for ≥2 years. A total of 242 patients (29%) were using glipizide at a dose ≥10 mg. A total of 137 patients had at least one ADR (16.5%); ADRs included: Hypoglycaemia (9.5%), haemolytic anaemia (3.6%) and common ADRs, including drug-induced fever, unspecified fever, nausea and vomiting, abnormal weight loss, throat pain, unspecified abnormal urine finding, specified disease of the stomach and duodenum, unspecified mood (affective) disorder, specified abnormal uterine and vaginal bleeding, asthma, and skin and subcutaneous haemangiomas (86.9%).

The results of the comparisons of the ADR rate by demographic and drug-related factors are presented in Table II. A significantly higher rate of ADRs was observed among the female patients (23%) vs. the male patients (11.6%) ($P<0.001$). Younger patients (aged <40 years) also had a significantly higher ADR rate (27.6%) vs. the other patients (>40 years of age) (15.7%) ($P=0.018$). The rate of ADRs did not differ significantly as regards the duration of medication or dose used ($P>0.05$).

The results from logistic regression analysis (Table III) revealed that a higher likelihood of developing adverse drug reactions was significantly associated with the female sex [odds ratio (OR), 2.40, $P<0.001$]. In addition, younger patients (aged <40 years) had a significantly higher rate of ADRs than older patients (>40 years of age; OR. 2.28, $P=0.01$). The duration of mediation and dose were not significantly related to ADRs ($P>0.05$).

Table I. Demographic and drug-related factors of the patients (n=830).

Characteristic	Value
Sex, n (%)	
Male	474 (57.1%)
Female	356 (42.9%)
Age (years)	
Mean ± SD	61.4±13.9
Median (IQR)	(54-71)
<40	58 (7.0%)
≥40	772 (93.0%)
Duration (months)	
Mean ± SD	25.7±19.0
Median (IQR)	24 (9.1-39.0)
<24	190 (22.9%)
≥24	640 (77.1%)
Dose (mg), n (%)	
<10	588 (70.8%)
≥210	242 (29.2%)
Adverse drug re-actions, n (%)	
Hypoglycaemia	13 (9.5%)
Haemolytic anaemia	5 (3.6%)
Common adverse drug reactions[a]	119 (86.9%)
Any adverse drug re-actions	
Yes	137 (16.5%)
No	693 (83.5%)

[a]Common adverse drug reactions included the following: Drug-induced fever; fever (unspecified), nausea and vomiting; abnormal weight loss; pain in throat; other and unspecified abnormal finding in urine; other specified disease of stomach and duodenum; unspecified mood (affective) disorder; other specified abnormal uterine and vaginal bleeding; abnormal uterine and vaginal bleeding (unspecified); asthma; haemangioma (skin and subcutaneous).

Discussion

Glipizide remains one of the main and highly prescribed treatments of T2DM. The results of the present study demonstrated that 137 patients developed glipizide-induced adverse reactions (16.5%); 9.5% developed hypoglycaemia, 3.6% developed haemolytic anaemia, 86.9% developed common adverse drug reactions. Both males and females developed adverse drug reactions; however, a greater number of female patients (23.0%) developed ADRs compared to the male patients (11.6%; $P<0.001$). It was also noted that the younger age group of patients whose age was <40 years had higher incidence of ADR (27.6%) compared to the older patients whose age was >40 years (15.7%; $P=0.018$). The dosage and duration of medication throughout which the medication was administered were not significant in relation to the ADRs ($P>0.05$).

The female body is built differently than that of a male in a number of ways; as a result, the way the body of a female responds differs from that of a male. Due to pharmacokinetics and pharmacodynamics, sex differences and the occurrence of certain adverse events are intertwined (15). For instance, the volume of distribution in females is less than that in males, which leads to the free fraction of the drug being higher in a female, which is also associated with a slower clearance of the medication from the body. The slower clearance of the drug is the reason why female patients could frequently be overdosed.

Table II. Adverse drug re-action rate by demographic and drug-related factors (n=830).

Factor	Total no. of patients	No. of patients with any ADR	%	P-value[a]
Demographic factors				
Sex				<0.001
Male	474	55	11.6	
Female	356	82	23.0	
Age (years)				0.018
<40	58	16	27.6	
≥40	772	121	15.7	
Drug-related factors				
Duration (months)				0.10
<24	190	39	20.5	
≥24	640	98	15.3	
Dose (mg)				0.15
<10	588	104	17.7	
≥10	242	33	13.6	

[a]Values were calculated using the Chi-squared test. ADR, adverse drug reaction.

Table III. Multivariate logistic regression model for any adverse drug reactions (n=830).

Factor	Percent	OR	95% CI	P-value
Sex				
Male	57.1%	1.00	Ref.	
Female	42.9%	2.40	(1.64-3.51)	<0.001
Age (years)				
<40	7.0%	2.28	(1.22-4.26)	0.010
≥40	93.0%	1.00	Ref.	
Duration (months)				
<24	22.9%	1.00	Ref.	
≥24	77.1%	0.70	(0.46-1.07)	0.10
Dose (mg)				
<10	70.8%	1.00	Ref.	
≥10	29.2%	0.75	(0.49-1.16)	0.19

OR, odds ratio, CI, confidence interval, Ref., Reference group.

Certain pharmacological factors affect females as well. These factors are the number of receptors, alteration in binding and alteration in signal transduction after the receptor binding (15). Moreover, the ionization of weak acids and bases in the gastroenteric tract is altered in patients with T2DM. The alteration in the ionization affects the absorption of certain drugs, such as glipizide (14).

Females are more susceptible to UTIs as the urethra of a female is shorter than that of a male. (18) Glycosuria, excess sugar levels in the urine, as a rule, allows several microbes to grow, leading to the development of UTIs (17). Some patients taking glipizide develop glycosuria, which is even more common among female patients >60 years of age (17).

To the best of our knowledge, the number of studies on glipizide-induced adverse effects in relation to age and sex published to date are limited worldwide, which suggests the importance of the present study. The strength of the present study lies in the number of patients taking glipizide, and the fact that the results demonstrated a higher likelihood of developing glipizide-induced adverse reactions in female patients and in patients aged <40 years. The aim of the present study was to shift the approach to personalized medicine rather than traditional medicine.

A limitation of the present study was the under-reporting of ADRs in KFSH&RC due to the lack of a system in place for this specific matter. ADRs are required to be reported in a systematic manner by physicians whenever they occur, particularly especially when life-threatening reactions occur.

In conclusion, the findings of the present study are comparable with those of other studies assessing the adverse reactions induced by glipizide. Recommendations for glipizide therapy include educating the patients on the possibility of developing adverse events, the likelihood of these occurring and routine monitoring to allow the detection of any abnormalities identified through the laboratory. These recommendations will help in dealing with current glipizide- induced adverse reactions and any future reactions that could occur. Moreover, the awareness on reporting any adverse reactions among physicians should be highly encouraged as soon as the doctors meet with their patients and are aware of the presence of any drug-induced adverse reactions. Increasing the amount of data recorded not only helps deal with the current situation to improve patientcare, but would also help prevent future severe adverse reactions from occurring.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed to conducting the study. HHS conceived and designed the study and carried out the project. THH assisted with the conception of the study and the brainstorming process, performed the literature review, went over the patients' files provided by the hospital, and wrote the proposal, abstract, and manuscript. HHS reviewed the proposal and wrote the manuscript as well. ANA and SNA obtained the data. The data analyses and tables were performed and prepared by RTB. The manuscript was reviewed by RAS. RAS also contributed to the conception of the study. HHS was the principal investigator and corresponding author. ANA and SNA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the office of Research Affairs of King Faisal Specialist Hospital and Research Centre on the November 5, 2021 (approval nos. RAC# 2211211 and 2235443). The requirement for patient consent was waived by the committee due to retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Glipizide: MedlinePlus Drug Information. Glipizide: MedlinePlus Drug Information. Available from: https://medlineplus.gov/druginfo/meds/a684060.html. Accessed at February 17, 2023.
2. Glipizide (Glucotrol): Generic, uses, side effects, dosage, interactions & warnings. RxList. Available from: https://www.rxlist.com/consumer_glipizide_glucotrol/drugs-condition.htm. Accessed at February 18, 2023.
3. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H and Martín C: Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 30: 6275, 2020.
4. Glipizide Oral: Uses, side effects, interactions, pictures, warnings & dosing-WebMD. Glipizide oral: Uses, side effects, interactions, pictures, warnings & dosing-WebMD. Available from: https://www.webmd.com/drugs/2/drug-10094-9061/glipizide-oral/glipizide-tablet-oral/details. Accessed at February 17, 2023.
5. Correa R, Rodriguez BS and Nappe TM. Glipizide-StatPearls-NCBI Bookshelf. Glipizide-StatPearls-NCBI Bookshelf. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459177/. Accessed at July 4, 2022.
6. Correa R: Glipizide, Available from: https://www.ncbi.nlm.nih.gov/books/NBK459177/. StatPearls, Treasure Island, FL, 2023.
7. de Wet H and Proks P: Molecular action of sulphonylureas on KATP channels: A real partnership between drugs and nucleotides. Biochem Soc Trans 43: 901-907, 2015.
8. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corlianò F, Fra GP, Bartoli E and Derosa G: Sulfonylureas and their use in clinical practice. Arch Med Sci 11: 840-848, 2015.
9. Glipizide: Uses, interactions, mechanism of action | DrugBank Online. (n.d.). Glipizide: Uses, Interactions, Mechanism of Action | DrugBank Online. Available from: https://go.drugbank.com/drugs/DB01067. Accessed at February 16, 2023.
10. Sagedal S, Asberg A, Hartmann A, Bergan S and Berg KJ: Glipizide treatment of post-transplant diabetes does not interfere with cyclosporine pharmacokinetics in renal allograft recipients. Clin Transplant 12: 553-556, 1998.
11. Chen L, Li JH, Kaur V, Muhammad A, Fernandez M, Hudson MS, Goldfine AB and Florez JC: The presence of two reduced function variants in CYP2C9 influences the acute response to glipizide. Diabet Med 37: 2124-2130, 2020.
12. Song J, Yang Y, Mauvais-Jarvis F, Wang YP and Niu T: KCNJ11, ABCC8 and TCF7L2 polymorphisms and the response to sulfonylurea treatment in patients with type 2 diabetes: A bioinformatics assessment. BMC Med Genet 18: 64, 2017.
13. Avery P, Mousa SS and Mousa SA: Pharmacogenomics in type II diabetes mellitus management: Steps toward personalized medicine. Pharmgenomics Pers Med 2: 79-91, 2009.
14. Seghieri G, Franconi F and Campesi I: Why we need sex-gender medicine: The striking example of type 2 diabetes. Diabetology 3: 460-469, 2022.
15. Soldin OP and Mattison DR: Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 48: 143-157, 2009.
16. Glipizide and Glycosuria-A Phase IV clinical study of FDA Data eHealthMe. Available from: https://www.ehealthme.com/ds/glipizide/glycosuria/. Accessed at May 24, 2024.
17. Prajapati AK: Urinary tract infection in diabetics, IntechOpen. Available from: https://www.intechopen.com/chapters/64419#:~:text=The%20presence%20of%20glycosuria%20is,patients%20with%20a%20complicated%20UTI. Accessed at May 24, 2024).
18. Urinary tract infections Urinary tract infections | Office on Women's Health. Available from: https://www.womenshealth.gov/a-z-topics/urinary-tract-infections#:~:text=Women%20get%20UTIs%20more%20often,is%20shorter%20than%20a%20man%27s. Accessed at May 24, 2024.
19. Ben-Omran T, Ghanim KA, Yavarna T, Akoum ME, Samara M, Chandra P and Al-Dewik N: Effects of consanguinity in a cohort of subjects with certain genetic disorders in Qatar. Mol Genet Genomic Med 8: e1051, 2020.