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Research letter

Comparison of hepatocellular carcinoma risk between patients treated with glimepiride and gliclazide

Introduction

Hepatocellular carcinoma (HCC) is among the most common cancers in the world, ranking fifth for men and eighth for women [1]. Age-adjusted incidence rates are high (> 20 per 100,000 men and > 10 per 100,000 women) in Africa and East Asia (including Korea, China and Taiwan), whereas the rates are low (< 5 per 100,000) in the US, Australia and Northern Europe [1,2].

Besides the common risk factors, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, liver cirrhosis (LC) and chronic alcohol abuse [1,2], the importance of obesity and type 2 diabetes mellitus (T2DM) as HCC risk factors has also been proposed [3]. Upon acknowledging the link between T2DM and HCC, many studies have gone on to investigate the effects of antidiabetes medications on incident HCC [4–6]. Metformin may reduce cancer incidence and cancer-related mortality by improving insulin resistance and activating cellular AMP-activated protein kinase [4,5]. However, the findings for thiazolidinedione exposures and HCC are conflicting [5,6]. On the other hand, the insulin secretagogue sulphonylurea has been associated with an increased cancer risk because it promotes insulin secretion [5,6].

Nevertheless, it remains unclear whether there is any difference depending on the type of sulphonylurea. For this reason, the present study has explored the association between two commonly used sulphonylureas (glimepiride and gliclazide) and the development of HCC.

Materials and methods

Study subjects

Patients with T2DM who were treated at the outpatients department of the Endocrinology Division, Severance Hospital, between 1 January 2008 and 31 December 2011 were retrospectively reviewed. Eligible patients were aged ≥ 20 years and had been prescribed either glimepiride or gliclazide for > 2 years. Excluded were patients for the following reasons: age < 20 years; a prescription history of both glimepiride and gliclazide; and a previous diagnosis of cancer. A total of 4459 patients (3044 glimepiride users and 1415 gliclazide users) were enrolled and followed for the development of HCC until 31 March 2016, with a median follow-up time of 7.8 years [interquartile range (IQR): 6.5–8.1 years].

Collection of clinical and laboratory data

Baseline data, including age, gender, medication use and comorbidities [chronic hepatitis B (CHB), chronic hepatitis C (CHC) and LC], were collected through a review of electronic medical records. Body weight, body mass index (BMI) and laboratory data at the time of initiation of either gliclazide or glimepiride were examined. Venous blood samples were taken after overnight fasting.

Incident HCC was defined as a final diagnosis of HCC (ICD-10-CM 22.0), according to European Association for the Study of Liver (EASL) diagnostic criteria [7]. To reduce any potential bias, patients diagnosed with HCC within 1 year of their first prescription of sulphonylurea were excluded.

Statistical analysis

Patients were compared for the development of HCC according to type of sulphonylurea. To obtain objective study groups, propensity score matching (PSM) was performed on baseline covariates. Details of propensity score distribution and standardized mean differences are shown in Figs. S1 and S2 (see supplementary materials associated with this article online). After PSM, 2580 patients (1290 glimepiride users and 1290 gliclazide users) were analyzed.

All continuous variables are presented as means ± standard deviation (SD), and categorical data are presented as numbers (percentages). Differences between glimepiride and gliclazide users were analyzed using Student's *t*-test or Chi^2 test. To identify the independent factors responsible for the development of HCC, univariate analysis was performed first. Multivariate logistic regression analyses were performed by adjusting for variables significant ($P < 0.05$) on univariate analyses. For all tests, a P value < 0.05 was considered significant. SPSS for Windows (version 20.0) software (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Table 1 shows baseline characteristics of the matched cohort. The mean age of subjects was about 62 years. Serum fasting plasma glucose (FPG) levels at initiation of sulphonylurea treatment were slightly higher in the glimepiride group, but there were no differences in baseline HbA_{1c} between the two groups. There were also no differences in liver panels or comorbidities (CHB, CHC, LC) either.

After a median follow-up of 7.8 (IQR: 6.5–8.1) years, 59 patients (2.3%) had newly developed HCC. The incidence of HCC was 3.0% (39/1290) in glimepiride users and 1.6% (20/1290) in gliclazide users, which was significantly higher with glimepiride ($P = 0.012$).

To analyze the factors associated with the incidence of HCC, logistic regression analyses were performed. On univariate

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Table 1
Baseline characteristics and development of hepatocellular carcinoma in patients treated with glimepiride or gliclazide.

Variables	Study patients ($n = 2580$)		
	Glimepiride ($n = 1290$)	Gliclazide ($n = 1290$)	*P*
Age, years	62.7 ± 10.4	62.4 ± 11.3	0.569
Male gender, *n* (%)	675 (52.3)	700 (54.3)	0.356
Body mass index, kg/m^2	25.1 ± 10.8	24.6 ± 3.5	0.520
HbA_{1c}, mmol/mol	58.0 ± 4.2	58.0 ± 4.2	0.977
HbA_{1c}, %	7.5 ± 1.3	7.5 ± 1.3	–
FPG, mmol/L	8.2 ± 2.9	7.9 ± 2.6	0.021
Total cholesterol, mg/dL	175.0 ± 41.3	172.6 ± 38.6	0.143
BUN, mg/dL	16.7 ± 6.6	17.6 ± 7.7	0.001
Creatinine, mg/dL	1.0 ± 0.4	1.1 ± 0.5	0.001
AST, IU/L	25.9 ± 29.8	25.9 ± 21.7	0.968
ALT, IU/L	28.4 ± 38.1	28.9 ± 28.6	0.707
Total bilirubin, mg/dL	0.7 ± 0.4	0.7 ± 0.3	0.715
Albumin, g/dL	4.5 ± 0.2	4.5 ± 0.2	0.671
Platelet count, $10^3/\mu L$	234.6 ± 82.6	230.5 ± 80.3	0.377
Prothrombin time, s	14.3 ± 9.8	14.3 ± 8.6	0.940
Chronic hepatitis B, *n* (%)	34 (2.6)	38 (2.9)	0.837
Chronic hepatitis C, *n* (%)	8 (0.6)	13 (1.0)	0.334
Liver cirrhosis, *n* (%)	64 (5.0)	70 (5.4)	0.604
Hepatocellular carcinoma, *n* (%)	39 (3.0)	20 (1.6)	0.012

analysis, the following were associated with an increased risk of HCC development (Table 2): male gender; CHB or CHC viral infection; presence of LC; use of glimepiride; $HbA_{1c} \geq 48$ mmol/mol (6.5%); aspartate aminotransferase (AST) ≥ 40 IU/L; alanine aminotransferase (ALT) ≥ 40 IU/L; and total bilirubin ≥ 2 mg/dL. After further adjustments for factors that were significant on univariate analyses, male gender, CHB, LC and elevated AST (≥ 40 IU/L) remained independent predictors of HCC incidence (all $P < 0.05$). Above all, the use of gliclazide was associated with a significantly lower risk of HCC [odds ratio (OR): 0.29; 95% confidence interval (CI): 0.15–0.58; $P < 0.001$].

A subgroup analysis further stratified patients based on gender. In men, cirrhosis and elevated liver enzymes were identified as predictive parameters for HCC development (Table S1; see supplementary materials associated with this article online). The use of gliclazide was shown to be a protective variable (OR: 0.33, 95% CI: 0.16–0.68; $P = 0.003$). In women, CHB and LC patients were strongly associated with HCC incidence, and gliclazide use had the lowest OR at 0.04 (95% CI: 0.01–0.84; $P = 0.038$).

Next, patients were stratified based on liver disease status (presence or absence of chronic liver disease, including CHB, CHC and LC). In the absence of chronic liver disease, being male and having an elevated AST (≥ 40 IU/L) were associated with a higher incidence of HCC (Table S2; see supplementary materials associated with this article online). Gliclazide use was negatively correlated with HCC, but this was not statistically significant ($P = 0.180$). In subjects with chronic liver disease, the use of gliclazide was associated with a lower incidence of HCC compared with glimepiride (OR: 0.26, 95% CI: 0.12–0.55; $P < 0.001$).

Discussion

In our retrospective PSM analysis, the long-term outcomes for incident HCC with glimepiride and gliclazide use were compared. In addition to well-known variables such as male gender, having CHB or LC, or elevated liver enzymes, gliclazide was shown to be associated with a lower incidence of HCC compared with glimepiride. In addition, the protective impact of gliclazide was more prominent in patients with chronic liver disease.

The results of previous studies comparing the impact of various sulphonylureas on HCC have been inconsistent. A nested case-control study by Kawaguchi et al. [6] showed that the second-generation sulphonylureas (gliclazide, glibenclamide) were associated with an increased overall cancer or HCC risk; however, this association was not observed with the third-generation sulphonylurea glimepiride. On the other hand, in a case-control study by Monami et al. [8], treatment with gliclazide for > 3 years was associated with a reduced cancer risk (OR: 0.40; $P = 0.004$), whereas glibenclamide was associated with an increased cancer risk (OR: 2.62; $P = 0.009$). Furthermore, in a large cohort study by Yang et al. [9], ever-use of gliclazide reduced the risk of cancer by 35% in a dose-dependent manner. Our present study results are in line with the latter findings: long-term gliclazide (≥ 2 years) had a protective effect on HCC development compared with glimepiride.

One possible explanation for this finding may be the innate characteristics of gliclazide, which is known to be a free-radical scavenger with, unlike other sulphonylureas, an aminoazabicyclo-octyl ring [10]. An experimental study showed the beneficial effects of gliclazide on DNA damage caused by free radicals in human peripheral blood lymphocytes and mouse insulinoma cells [11]. The drug was also effective for attenuating DNA damage triggered by hydrogen peroxidase in both T2DM and non-diabetic subjects, suggesting the potential role of gliclazide in reducing the risk of oxidative stress-linked chronic diabetes complications, including cancer [12].

Patients with T2DM have increased oxidative stress-related DNA damage and a diminished ability to repair DNA, which makes them susceptible to DNA mutations and neoplastic transformations [13]. Thus, gliclazide may have better clinical outcomes in the

Table 2
Logistic regression analyses for incidence of hepatocellular carcinoma.

Variable	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (≥ 65 years)	0.65	0.38–1.11	0.115	1.12	0.57–2.19	0.750
Gender (female)	0.17	0.08–0.37	< 0.001	0.28	0.12–0.66	0.003
BMI (≥ 25 kg/m^2)	0.50	0.20–1.21	0.122			
Chronic hepatitis B	22.15	12.03–40.76	< 0.001	3.51	1.49–8.27	0.004
Chronic hepatitis C	4.63	1.05–20.33	0.043	1.99	0.30–13.30	0.477
Liver cirrhosis	71.85	39.01–132.36	< 0.001	34.80	16.88–71.74	< 0.001
Gliclazide use	0.50	0.29–0.87	0.014	0.29	0.15–0.58	< 0.001
HbA_{1c} (≥ 48 mmol/mol)	0.56	0.33–0.96	0.035	0.71	0.36–1.42	0.335
FPG (≥ 7.0 mmol/L)	0.93	0.55–1.59	0.803			
AST (≥ 40 IU/L)	6.34	3.65–11.01	< 0.001	3.64	1.75–7.57	0.001
ALT (≥ 40 IU/L)	3.53	2.05–6.09	< 0.001			
Total bilirubin (≥ 2 mg/dL)	6.83	1.49–31.26	0.013	0.45	0.06–3.12	0.418
Prothrombin time (≥ 14 s)	1.39	0.59–3.30	0.457			

Adjusted for age, gender, chronic hepatitis B, chronic hepatitis C, liver cirrhosis, HbA_{1c} (≥ 48 mmol/mol), AST (≥ 40 IU/L), total bilirubin (≥ 2 mg/dL). OR: odds ratio; CI: confidence interval; BMI: body mass index; HbA_{1c}: glycated haemoglobin; FPG: fasting plasma glucose; AST/ALT: aspartate/alanine aminotransferase.

development of HCC by protecting DNA against oxidative stress damage while improving DNA repair [11,12]. In addition, our present study has revealed that the protective effects of gliclazide differed according to the presence or absence of liver disease, being more evident in those with chronic liver disease. As high-risk patients experience unfavourable conditions caused by the constant inflammatory situation in the liver [2], they may benefit more from long-term gliclazide exposure.

The renoprotective effects of gliclazide compared with glimepiride have previously been reported in T2DM patients [14]. This might explain the higher baseline blood urea nitrogen (BUN) and creatinine levels in our gliclazide group. In addition, of our 2580 patients with T2DM, 59 were identified as having incident HCC (2284/100,000 population). This incidence rate is considerably higher than that of the general population, and may be due to the characteristics of our study participants: all patients had T2DM, and it is well known that the development of chronic liver disease or HCC is likely to increase two- to threefold in such patients [3]. Furthermore, although the prevalence of LC is unknown, the US National Health and Nutrition Examination Survey (NHANES) found an LC prevalence of 0.27% [15], which is far below the 5.2% observed in the present study. As our institution is a university-affiliated hospital, selection bias may have occurred, with the higher prevalence of LC leading to the increased incident rate of HCC.

Our study also has some other limitations. First, the potentially confounding factors that could have influenced HCC incidence, such as alcohol intakes and smoking, were not assessed. Second, the dose of each sulphonylurea was not known and, third, it was not possible to consider the effects of other antidiabetic medications, such as metformin, thiazolidinediones and exogenous insulin. However, a relatively large study population was analyzed to compare relationships between the most commonly used sulphonylureas and the development of HCC.

In conclusion, our analysis has demonstrated that gliclazide is associated with a lower incidence of HCC compared with glimepiride. Also, the protective effects of gliclazide were more prominent in patients with chronic liver disease. Further prospective studies are now warranted to increase our understanding of the relationship between antidiabetic drugs and HCC.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Figs. S1 and S2, and Tables S1 and S2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2017.06.007.

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