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Original Research Article

Correlation of various lipid-lowering and hypoglycemic drugs with the risk of gastric cancer in elderly population

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Abstract

Purpose: *To investigate the correlation between several lipid-lowering and hypoglycemic drugs and the risk of gastric cancer (GC) in elderly population.*
Methods: *A total of 160 elderly patients with GC who attended The First Affiliated Hospital of Henan University of Science and Technology from January 1, 2014 to December 31, 2020 were enrolled in the study group. Furthermore, 320 healthy volunteers within the same period were assigned to the control group. Clinical data (such as history of statin, sulfonylurea and biguanide administration) were collected from the patient's medical records. Multifactorial logistic regression was used to determine the association between these lipid-lowering and glucose-lowering drugs, and the risk of developing GC.*
Results: *After adjusting for numerous confounding factors, multifactorial logistic regression showed that long-term use (>12 months of treatment) of statins and biguanides significantly reduced the risk of GC in elderly population (p = 0.006, p = 0.004, respectively), while long-term use of sulphonylureas increased the risk of GC in elderly population (p = 0.004).*
Conclusion: *Statins, sulfonylureas and biguanides may be closely associated with the development of GC in elderly population. Therefore, a detailed understanding of the efficacy and mechanisms of action of these drugs may benefit the elderly in the prevention and control of GC.*

Keywords: *Gastric cancer, Statins, Sulfonylureas, Biguanides, Association*

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INTRODUCTION

In 2019, the morbidity rate of gastric cancer (GC) in China was 43.1 in 100,000, the second highest of all malignancies, and the mortality rate was 29.6 in 00,000, the third highest of all malignancies, both of which are well above the world average [1,2]. At the same time, older people over 60 years of age are considered to be at a higher risk of suffering from this malignancy [1,3]. In this population, there are several challenges to the prevention and treatment of GC. For example, the early stages of GC in the elderly often lacks typical symptoms and ageing leads to a reduced tolerance to disease and treatment [4]. As a result, elderly patients with GC are often diagnosed late, experience more treatment limitations, and have a significantly

poorer prognosis compared to middle-aged patients. In the light of this situation, a comprehensive epidemiological study of GC patients in the elderly population is a valuable solution to understand the various harmful or protective factors associated with the tumor and reduce its incidence at source.

It is well known that lipid-lowering and hypoglycaemic drugs are two classes of drugs commonly used in the elderly. Studies outside China have shown that statin lipid-lowering drugs have a protective effect against GC, but this effect may vary among regions and populations [5,6]. Other studies have also shown that the hypoglycaemic drug, metformin may reduce the risk of developing GC [7,8]. However, other studies are inconsistent with the above finding, suggesting that this hypoglycaemic drug may simply influence the course of GC and that bias amplified the association of this drug with tumors [9-11]. One study also suggested that sulfonylurea hypoglycaemic drugs might increase the risk of GC, but there was no follow-up report to support this [7]. Therefore, research on the effect of lipid-lowering and hypoglycaemic drugs on the risk of GC is still inconclusive, and there are still several limitations in terms of depth and breadth.

However, studies in this area in China are still in their infancy, with few studies reported specifically on the elderly. Therefore, the present study included hundreds of elderly patients with GC and healthy control subjects, to determine the association between various lipid-lowering and hypoglycaemic drugs and the risk of GC in the elderly population.

METHODS

Clinical samples

One hundred and sixty elderly patients with GC who attended the First Affiliated Hospital of Henan University of Science and Technology from January 1, 2014 to December 31, 2020 were selected to participate in this study. The inclusion criteria were as follows: (1) patients with pathologically-confirmed GC who were diagnosed at an age > 60 years old, regardless of gender; (2) Those in whom no other malignant neoplasm had developed; (3) patients with complete medical records, and a clear history of previous illnesses and medication taken; and (4) patients who agreed to participate in the study and sign informed consent form. A total of 320 healthy subjects were randomly selected from the medical examination department of the hospital during the same period to serve as controls.

Inclusion criteria

They are as follows: (1) Controls were selected according to a ratio of 1:2; (2) As there were significantly more men than women with GC, controls were required to match each group in terms of gender; (3) No previous malignancy of any type; (4) History of previous illnesses as well as medication history were clearly documented in the medical history of the examination; (5) Those who agree to participate in this study and sign the informed consent form.

Exclusion criteria

Patients who did not meet the above inclusion criteria.

Ethical matters

This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology(202203B060) and followed the guidelines of the World Medical Association Declaration of Helsinki [12].

Data collection

Data were collected using a pre-designed data collection form which captured the following: gender, age, ethnicity, history of smoking, alcohol consumption, gastric polyps, gastric ulcers, *Helicobacter pylori* (HP) infection, type 2 diabetes mellitus (DM), high total cholesterol (TC) and high triglycerides (TG). Others are obesity and overweight, coronary heart disease (CHD), stroke and history of statins, betablockers, sulphonylureas, glinides, α-glucoside inhibitors and other lipid-lowering drugs. A history of lipid-lowering glucose medications such as statins, fibrates, sulfonylureas, glinides, biguanides, and alpha-glucosidase inhibitors were also included.

A history of smoking was defined as a lifetime of regular smoking for at least 12 months, with no limit on the quantity of cigarettes smoked per day. History of alcohol consumption was defined as regular alcohol consumption for at least 12 months of a lifetime, with no limit on the amount of alcohol consumed per day. Obesity and overweight were defined as conditions preceding the development of GC and were determined as body mass index, with a body mass index between 24.0 and 27.9 kg/m^2 defined as overweight, and greater than 28.0 kg/m^2 defined as obese [13]. The history of various chronic

diseases was determined using the 'principal diagnosis' in the medical records and the history of relevant treatment. The history of various lipid-lowering and blood glucose medications, including the specific type, mode of administration and duration of treatment, was obtained by reviewing the medical records or contacting the subject by telephone. In particular, continuous or cumulative duration of treatment for more than 12 months was defined as "long-term use".

Data analysis

Normally distributed continuous variables are expressed as arithmetic mean ± standard deviation (SD), while differences between two continuous variables were assessed using independent sample t-checks, with t-values and *p*-values reported. Categorical variables were then expressed as frequency and composition ratios, while differences between two categorical variables were analyzed and assessed via chi-square test, with results reported as χ^2 values and *p*-values. Multifactorial logistic regression was conducted to analyze the association between a range of potentially influencing factors and the risk of GC. It was adjusted for gender, age, ethnicity, history of smoking and alcohol consumption, gastric polyps, gastric ulcers, HP infection, type 2 DM, hyperlipidaemia, obesity, CHD, stroke and history of multiple lipid and glucose-lowering medications. The results are reported as ratio (OR), 95 % confidence interval (95 % CI) and *p*-values. In this regard, $p < 0.05$ was defined as statistically significant.

RESULTS

Baseline characteristics and medical history of elderly GC patients

As shown in Table 1, subjects in study group were older than those in control ($p = 0.014$). A higher proportion of subjects in study group had never smoked and consumed alcohol compared to those in control group ($p = 0.025$, $p = 0.013$), and subjects in the treatment group were also more likely to have had previous gastric polyps, gastric ulcers, HP infection, and obesity ($p = 0.007$, $p = 0.001$, $p < 0.001$, $p = 0.023$). In addition, there were no differences between two groups of subjects with regard to gender, ethnicity, type 2 DM, hypertriglyceridaemia, hypercholesterolaemia, overweight, CHD, or history of stroke ($p > 0.05$).

Medication history in healthy control groups of elderly GC patients

As shown in Table 2, the proportion of patients in study group who had taken a statin was significantly smaller than that in control group ($p = 0.007$). In contrast, the proportions of betablockers, sulphonylureas, glinides, biguanides and alpha-glucosidase inhibitors taken in two groups were not statistically different ($p > 0.05$).

This study also screened out subjects on medication for > 12 months for separate analysis, with the result that a lower proportion of subjects in study group were on long-term (> 12 months)

Table 1: Baseline characteristics and medical history of geriatric GC patients

Group	Total (n, %)	Male (n, %)	Age (n, %)	Han ethnicity (n, %)	Smoking (n, %)	Alcohol (n, %)	Gastric polyps (n, %)	Gastric ulcers (n, %)
Study group	160 (100.0)	112 (70.0)	68.4±4.5	152 (95.0)	33 (20.6)	37 (23.1)	30 (18.8)	21 (13.1)
Control group	320 (100.0)	203 (63.4)	67.3±4.7	292 (91.3)	41 (12.8)	45 (14.1)	32 (10.0)	15 (4.7)
t/χ2 value	-	2.036	2.465	2.162	4.993	6.185	7.260	10.946
P value	-	0.154	0.014	0.141	0.025	0.013	0.007	0.001

Group	HP (n, %)	type 2 DM (n, %)	High TG (n, %)	High TC (n, %)	Obesity (n, %)	Overweight (n, %)	CHD (n, %)	Stroke (n, %)
Study	75 (46.9)	42 (26.3)	35 (21.9)	42 (26.3)	27 (16.9)	67 (41.9)	57 (35.6)	15 (9.4)
Control	34 (10.6)	70 (21.9)	63 (19.7)	61 (19.1)	31 (9.7)	118 (36.9)	97 (30.3)	34 (10.6)
t/χ^2 value	79.860	1.141	0.314	3.270	5.187	1.126	1.382	0.182
P value	＜0.001	0.285	0.575	0.071	0.023	0.289	0.240	0.670

Note: Continuous variables conforming to the normal distribution was displayed as mean ± SD. Categorical variables were shown as frequencies (composition ratios) and differences were evaluated by applying chi-square test, reporting χ2 and *p* values

Table 2: Comparison of medication history between study and control groups

Variable	Study group (n, %)	Control group (n, %)	*χ2*	*P*-value
Statins				
Total	57 (35.6)	166 (51.9)	7.268	0.007
duration ≥ 12 months	29 (18.1)	98 (30.6)	8.566	0.003
Betablockers,				
Total	11 (6.9)	18 (5.6)	0.294	0.588
duration ≥ 12 months	6 (3.8)	5 (1.6)	2.280	0.131
Sulphonylureas				
Total	21 (13.1)	33 (10.3)	0.845	0.358
duration ≥ 12 months	17 (10.6)	15 (4.7)	6.044	0.014
Glinides				
Total	16 (10.0)	29 (9.1)	0.110	0.740
Duration ≥ 12 months	11 (6.9)	24 (7.5)	0.062	0.804
Biguanides				
Total	26 (16.3)	61 (19.1)	0.569	0.451
Duration ≥ 12 months	15 (9.4)	55 (17.2)	5.226	0.022
Alpha-glucosidase inhibitors				
Total	17 (10.6)	30 (9.4)	0.189	0.664
Duration ≥ 12 months	11 (6.9)	18 (5.6)	0.294	0.588

Table 3: Multifactorial logistic regression of the association between history of multiple chronic diseases and risk of GC in elderly population

Variable	B	SE	Wald χ2	OR	95%CI	*P*-value
Type 2 DM	0.192	0.230	0.700	1.212	0.773 ~ 1.902	0.403
High TG	0.168	0.245	0.472	1.183	0.732 ~ 1.911	0.492
High TC	0.420	0.234	3.223	1.523	0.962 ~ 2.409	0.073
Obesity	0.784	0.303	6.711	2.190	1.210 ~ 3.963	0.010
Overweight	0.380	0.212	3.195	1.462	0.964 ~ 2.217	0.074
CHD	0.203	0.209	0.950	1.225	0.814 ~ 1.845	0.330
Stroke	-0.108	0.332	0.106	0.897	0.468 ~ 1.720	0.744

Note: Multifactorial logistic regression adjusted for sex, age, ethnicity, history of smoking and alcohol, history of gastric polyps, history of gastric ulcers, history of *H. pylori* infection, type 2 DM, hyperlipidaemia, obesity and overweight, CHD, stroke, and history of multiple lipid and glucose-lowering medications

statin lipid-lowering and biguanide hypoglycaemic drugs than in control group (p = 0.003, p = 0.022), while a higher proportion of subjects were on long-term sulphonylurea hypoglycaemic drugs than in control group (p = 0.014).

Association of a history of multiple chronic diseases with the risk of GC in elderly population

As shown in Table 3, after adjusting for the aforementioned potential confounders, multifactorial logistic regression revealed a significant association between a previous history of obesity and increased risk of GC (OR = 2.190, 95 % CI = 1.210 to 3.963, p = 0.010). In addition, multifactorial logistic regression indicates any association between type 2 DM, hypertriglyceridaemia, hypercholesterolaemia, overweight, CHD, and history of stroke and risk of GC (p > 0.05).

Association between a history of multiple lipid-lowering and hypoglycemic drug use and risk of GC in elderly population

As shown in Table 4, after adjusting for the aforementioned potential confounders, multifactorial logistic regression revealed a significant association between previous statin use and a decreased risk of GC (OR = 0.515, 95 % CI = 0.347 ~ 0.764, p = 0.001). Multi-factorial logistic regression also indicated that previous use of betablockers, sulphonylureas, glinides, biguanides and alpha-glucosidase inhibitors were not linked to the risk of GC (p > 0.05).

Correlation between the history of in-take of multiple lipid-lowering and hypoglycemic drugs (long-term use) and the risk of GC in elderly population

After adjusting for the aforementioned potential confounders, multifactorial logistic regression

Table 4: Multifactorial logistic regression of the association between history of multiple lipid-lowering and hypoglycemic medication use and risk of GC in elderly population

Variable	B	SE	Wald χ2	OR	95%CI	*P*-value
Statins	-0.663	0.201	10.851	0.515	0.347 ~ 0.764	0.001
Betablockers	0.196	0.413	0.226	1.217	0.542 ~ 2.731	0.635
Sulphonylureas	0.616	0.382	2.594	1.851	0.875 ~ 3.915	0.107
Glinides	0.317	0.379	0.702	1.374	0.653 ~ 2.887	0.402
Biguanides	-0.615	0.378	2.651	0.541	0.258 ~ 1.134	0.104
α-Glucosidase inhibitors	0.256	0.427	0.358	1.291	0.559 ~ 2.981	0.549

Multifactorial logistic regression adjusted for sex, age, ethnicity, history of smoking and alcohol, history of gastric polyps, history of gastric ulcers, history of *H. pylori* infection, type 2 DM, hyperlipidaemia, obesity and overweight, CHD, stroke, and history of multiple lipid and glucose-lowering medications

Table 5: Multifactorial logistic regression of the association between history of multiple lipid-lowering and hypoglycemic drug use (long-term use) and risk of GC in the elderly population

Variable	B	SE	Wald χ2	OR	95%CI	*P*-value
Statins	-0.674	0.243	7.681	0.510	0.316 ~ 0.821	0.006
Betablockers	0.541	0.670	0.652	1.718	0.462 ~ 6.395	0.419
Sulphonylureas	1.220	0.418	8.513	3.388	1.493 ~ 7.688	0.004
Glinides	0.126	0.449	0.079	1.134	0.470 ~ 2.736	0.779
Biguanides	-1.071	0.373	8.255	0.343	0.165 ~ 0.711	0.004
Statins	0.355	0.500	0.502	1.426	0.535 ~ 3.801	0.479

***Note*:** Multifactorial logistic regression adjusted for sex, age, ethnicity, history of smoking and alcohol, history of gastric polyps, history of gastric ulcers, history of *H. pylori* infection, type 2 DM, hyperlipidaemia, obesity and overweight, CHD, stroke, and history of multiple lipid and glucose-lowering medications

found that previous (long-term) use of statins and biguanides was significantly associated with a reduced risk of GC. Previous (long-term) use of sulphonylureas was significantly associated with an increased risk of GC.

As shown in Table 5, after adjusting for the aforementioned potential confounders, multifactorial logistic regression found that previous (long-term) use of statins and biguanides was significantly correlated with a reduced risk of GC (OR = 0.510, 95 % CI = 0.316 ~ 0.821, p = 0.006; OR = 0.343, 95 % CI = 0.165 ~ 0.711, p = 0.004). Previous (long-term) use of sulphonylureas was significantly associated with an increased risk of GC (OR = 3.388, 95 % CI = 1.493 ~ 7.688, p = 0.004). Multi-factorial logistic regression also suggested that previous use of betablockers, glinides, and alpha-glucosidase inhibitors was not related to the risk of GC (p > 0.05).

DISCUSSION

Statins are used as important therapeutic agents in a variety of diseases such as hyperlipidaemia, CHD and ischaemic strokes. These drugs not only have definite lipid-lowering effects (especially blood cholesterol), but also stabilise large atheromatous plaques and prevent accidental plaque rupture. The beta-lipid-lowering drugs are the first-line agents for lowering blood triglyceride levels. Sulphonylureas, glinides, biguanides and alpha-glucosidase inhibitors are some of the most commonly used oral hypoglycaemic drugs in patients with type 2 DM [14]. With the increasing prevalence of the aforementioned cardiovascular and metabolic diseases among the elderly, these drugs are being taken more frequently by the elderly. Therefore, exploring the effects of these medications on the risk of GC will not only guide the improvement of health education and behavioural intervention strategies for the elderly population, but also contribute to an in-depth understanding of the pathogenesis of GC.

Based on the results of this study, researchers found that previous use of statin lipid-lowering drugs, sulfonylurea and biguanide hypoglycaemic drugs may affect the risk of GC among the elderly. Specifically, long-term or short-term use of statins reduced the risk of GC by approximately 50 %, while long-term use of biguanides reduces the risk of this tumor by approximately 60 % to 70 %. Furthermore, long-term use of sulphonylureas may increase risk of GC by approximately two-fold. Notably, short-term use of biguanides and sulphonylureas had no significant effect on the risk of developing GC. These results suggest that the effect of these three classes of drugs on the risk of developing GC is likely to be significant and it may have a dose-effect relationship.

The most prominent indications for statins, sulphonylureas and biguanides, such as

hyperlipidaemia, obesity, CHD, ischaemic stroke and type 2 DM, are clearly 'natural' confounders for this study. Therefore, researchers examined the association between these chronic diseases and GC, in order to assess the extent to which confounding factors influenced the results. These results showed that obesity increased the risk of GC by approximately 1-fold, while other chronic diseases had no significant effect on the risk of GC. In addition, multifactorial logistics analysis was conducted to adjust for these chronic disease histories and some other factors that were unevenly distributed across the two study groups (e.g. age) in order to obtain more reliable results.

The above findings are in line with some of the epidemiological findings from outside China [5-8]. Moreover, several more in-depth studies have been carried out by some scholars. For example, two studies confirmed that statins modulate the virulence factors of HP and inhibit the production of reactive oxygen species (ROS). Since both HP and oxidative stress are important promoters of gastric carcinogenesis, these findings partly explain the mechanism involved in the protective effect of statins against this malignancy [15,16]. Other experiments *in vitro* have shown that metformin combined with oxaliplatin or miR-365 inhibit the value added, and promote apoptosis in various GC cell lines such as SGC7901 and SNU-16 [17,18]. Animal experiments have demonstrated that Metformin enhance the therapeutic effects of rapamycin and cisplatin in mouse models of GC [19]. These results further support the findings of this study from different perspectives.

Administration of sulfonylureas leading to an increase in the risk of GC still requires further confirmation. This result is consistent with the results of a large sample size of an epidemiological study conducted outside China [7]. However, it should be stressed that sulphonylureas have been used for several years and their safety has not been questioned. Some of these basic studies have also investigated the effects of these drugs on other tumors, and they have shown that sulphonylureas inhibit the growth of blood vessels in malignant tumors such as breast and bladder cancer, and have a protective effect [20, 21]. Therefore, the effect of sulfonylureas on GC needs to be confirmed by further studies.

To the best of our knowledge, the present study is the first epidemiological study in China to provide a comprehensive analysis on this topic. Moreover, it focused on the elderly population and took into account the effect of different courses of drugs on the outcome. It also considered the effect of chronic diseases associated with these drugs on the outcome. Hence, the conclusions derived are reliable and could be an important basis for further studies.

Limitations of this study

First, the sample size was small due to objective constraints which reduced the validity of the statistical analysis. However, the results of this study are supported by a number of relevant studies, which somewhat alleviated our concerns about this shortcoming. Secondly, although the study analyzed each of the major drug classes separately, there may be differences in the mechanism of action and efficacy of various drugs within the same class. Moreover, the effects of each drug on GC were not revealed in this study. However, the present study will aid future studies with large sample sizes to focus and clarify research direction and achieve more accurate conclusions.

CONCLUSION

A variety of lipid-lowering and hypoglycaemic drugs commonly used in the elderly population (statins, sulphonylureas and biguanides) are likely to have effects on the risk of GC. Specifically, the use of statins and biguanides may protect against GC, whereas the use of sulphonylureas may be detrimental to the prevention and control of GC. In-depth studies on the efficacy and mechanisms of these drugs have the potential to reveal their new uses in the management of GC, and will contribute to the development of newer therapies for GC. Ultimately, this may help to reduce the incidence and mortality rate of GC among the elderly population.

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the

current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Zhiye Zhang and Wenzhong Xu conceived and designed the study; Zhiye Zhang, Liang Fang and Shuangshuang Guo collected and analyzed the data, while Zhiye Zhang wrote the manuscript which was approved by all the authors for publication.

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