ORIGINAL ARTICLE

Glyburide and risk of melioidosis in type 2 diabetes: a case-control study

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ABSTRACT

OBJECTIVE

To identify the association between glyburide and risk of melioidosis in patients with type 2 diabetes.

METHODS

We performed a case-control study of 68 case patients with preexisting type 2 diabetes and melioidosis infection and 359 control patients with preexisting type 2 diabetes without melioidosis to evaluate and compare the risk of melioidosis in type 2 diabetes of those with and without glyburide use. Logistic regression analysis was used for the case control comparison.

RESULTS

Patients who current user of glyburide had a non-significantly increased risk of melioidosis (crude odds ratio, 1.53; 95% confidence interval (CI), 0.89 to 2.63; further adjusted by sex, age, history of diabetic treatment and hypertension did not alter this result: adjusted odds ratio (AOR), 0.98; 95% CI, 0.48 to 2.02) but only hypertension was associated with lower risk of melioidosis (AOR, 0.30; 95% CI, 0.17 to 0.53). In the subgroup analysis, we found no significant association between glyburide, other sulfonylureas, metformin, insulin and first diagnosis of melioidosis. Moreover, we also found that chronic kidney disease was significantly associated with lower risk melioidosis.

CONCLUSION

We concluded that glyburide use was not associated with the risk of developing melioidosis among type 2 diabetic patients and we did not found an association between other antidiabetic drugs and risk of melioidosis as well.

INTRODUCTION

Melioidosis is a serious infection and epidemic in the Northeastern Thailand and the Northern Australia with the crude case fatality rate between 19% and 43%.[1,2] In Thailand, the annual incidence rate rose from 8.0 case per 100,000 people in 2000 to 23.1 in 2006.[1] The evidence from a case-control and a population-based studies in Thailand and Australia showed that 37-60% of the patients with melioidosis were also had type 2 diabetes.[3]

The majority of diabetic patients with melioidosis are already receiving antidiabetic therapy and glyburide is one of the oral hypoglycemic agents that commonly has been used in many countries.[4,5] One recent study showed that glyburide may control modulating capabilities on host immune response by inhibiting the production of active interleukin (IL)-1b and IL-18.[4] Moreover, a cohort study in 2011 found the benefit of glyburide in reducing the mortality rate of melioidosis.[6] But another cohort study in 2014 found that using sulphonylurea in diabetic patients with melioidosis may make patients to the higher risk for adverse outcomes.[7] However, the risk of developing melioidosis in type 2 diabetic patients who prescribed with glyburide has not been evaluated.Thus, we conducted a case-control study to calculate and compare the risks of melioidosis in type 2 diabetes with and without glyburide treatment.

METHODS

STUDY DESIGN

This case-control study was conducted using data from the medical records of the case and control patients who admitted at Khon Kaen Hospital, Thailand from January 2011 to August 2014.

STUDY POPULATION

We included case patients with the following criteria; (i) patients with melioidosis infection confirmed by positive culture for *B. pseudomallei*[3], (ii) patients who had a documentary of preexisting type 2 diabetes (fasting plasma glucose≥126 mg/dL or random venous plasma glucose≥200 mg/dL in a patient with classic symptoms of hyperglycemia or plasma glucose≥200 mg/dL measured two hours after a glucose load of 1.75 g/kg (maximum dose of 75 g) in an oral glucose tolerance test (OGTT) or hemoglobin A1C≥6.5 percent (47 mmol/mol))[7], and (iii) age 15 years or older. We excluded those without data using glyburide. For the control patients, we randomly selected four controls to one case matched by age and sex from those admitted at same study period with a laboratory confirmation of no *B. pseudomallei* infection. In addition to this, they must have to be confirmed diagnosed of preexisting type 2 diabetes using the criterion given above as well.

EXPOSURE AND CONFOUNDERS

Glyburide use was reviewed from the medical records of the case and control patients.

The most recent dosage of glyburide was also collected. Other exposures included other sulfonylureas, metformin, insulin were also reviewed and collected. The potential confound included sex, age, chronic kidney disease, nephrolithiasis, chronic liver disease, hypertension, body mass index, glycated hemoglobin, triglyceride, HDL cholesterol, and hemoglobin.

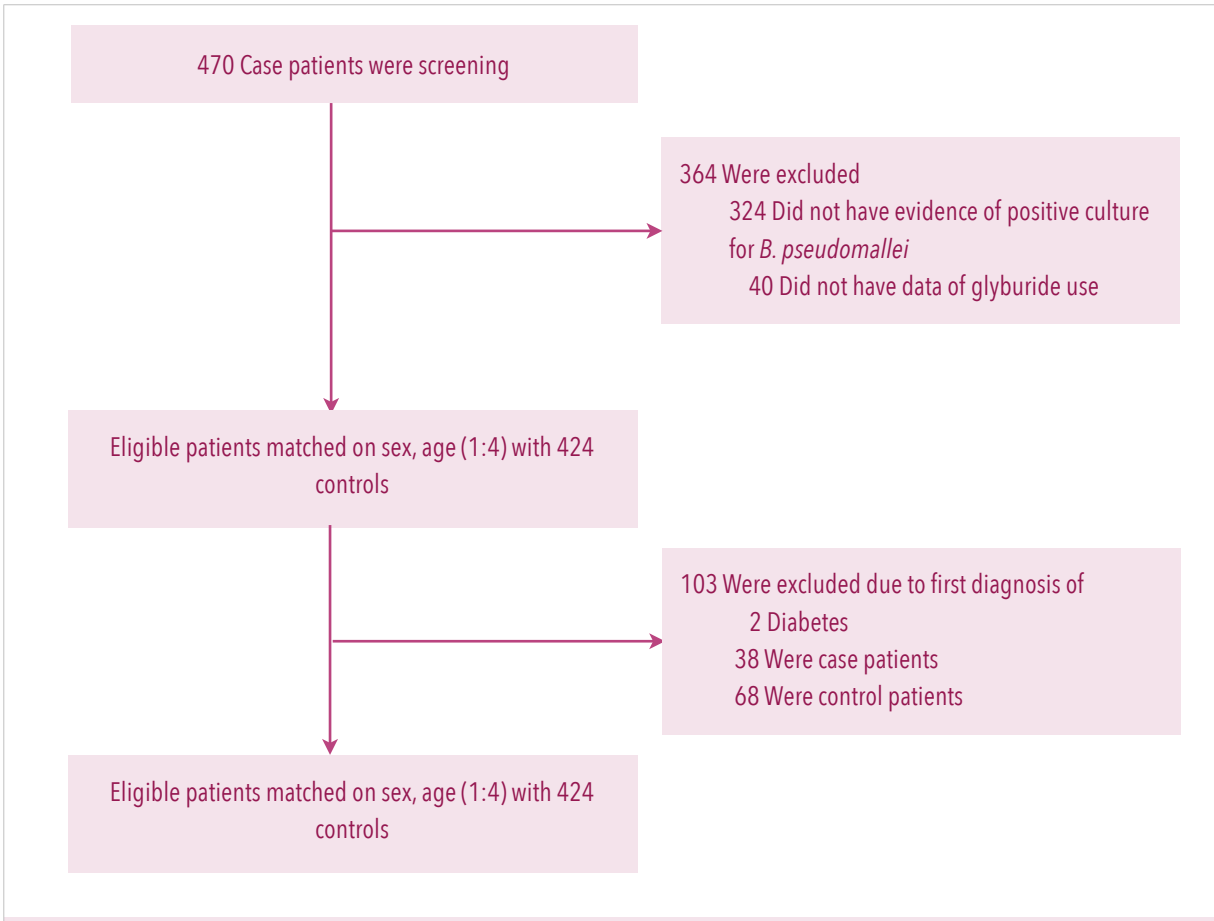


Figure 1. Selection of People to Include as Cases and Controls in Study of Glyburide and Risk of Melioidosis in Type 2 Diabetes.

HbA1c using the latest result for calculation. CKD is defined as abnormalities of kidney structure or function, present for 3 month; Markers of kidney damage (one or more) (i) Albuminuria (AER 30 mg/24 hours; ACR 30 mg/g [3 mg/mmol]), (ii) urine sediment abnormalities (iii) electrolyte and other abnormalities due to tubular disorders, (iv) abnormalities detected by histology, (v) structural abnormalities detected by imaging, (vi) history of kidney transplantation, and (vii) decreased GFR GFR <60 ml/min/1.73 m^2. Chronic liver disease was diagnosed from liver biopsy and clinical, laboratory test and radiologic data. Anemia was diagnosed by initial laboratory studies. Malignancy had to be from official pathologic reported by pathologist. Nephrolithiasis was diagnosed by radiologic evidence. Metabolic syndrome was defined as the presence of any three of the following five traits (i) abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in), (ii) serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug

Table 1. Characteristics, Crude Odds Ratio and Adjusted Odds Ratio of Patients with Melioidosis and Control Patients

Characteristic	Case Patients	Control Patients	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio(95% CI)
Male – no. (%)	50 (73.5)	260 (72.4)	1.06 (0.59-1.90)	1.08 (0.58-1.99)
Age – yr				
Median	53.5	54.7	0.99 (0.96-1.01)	1.00 (0.97-1.03)
Interquartile range	45.5-59.3	47.4-60.8		
History of diabetic treatment– no. (%)				
Glyburide	25 (36.8)	99 (27.6)	1.53 (0.89-2.63)	0.98 (0.48-2.02)
Other sulfonylurea	15 (22.1)	76 (21.2)	1.05 (0.56-1.97)	0.87 (0.39-1.94)
Metformin	41 (60.3)	150 (41.8)	2.11(1.25-3.59)	1.90 (1.03-3.50)
Insulin	15 (36.8)	132 (22.1)	0.49 (0.26-0.90)	0.65 (0.30-1.41)
Chronic kidney disease	5/64 (7.8)	94/314 (29.9)	0.20 (0.08-0.51)	–
Nephrolithiasis– no./total no. (%)	4/37 (10.8)	23/128 (18.0)	0.55 (0.18-1.72)	–
Chronic liver disease– no./total no. (%)	7/61 (11.5)	35/218 (16.1)	0.68 (0.29-1.61)	–
Hypertension – no. (%)	19 (27.9)	204 (56.8)	0.29 (0.17-0.52)	0.30 (0.17-0.53)
Body mass index – kg/m^2				
No. of patients with data of weight and height	23	111		
Body mass index	21.53.2	24.84.7	0.84 (0.74-0.94)	–
Glycated hemoglobin% – no./total no. (%)	12/13 (92.3)	42/67 (62.7)	7.14 (0.88-58.29)	–
Triglyceride– mg/dL				
No. of patients with data of triglyceride	7	50		
Median	181	128	1.00 (1.00-1.01)	–
Interquartile range	95.0-348.0	97.0-160.3		
HDL cholesterol-mg/dL				
No. of patients with data of HDL cholesterol	5	40		
HDL cholesterol	22.419.1	36.213.5	0.92 (0.85-1.00)	–
Hemoglobin – g/dL				
No. of patients with data of hemoglobin level	49	234		
Hemoglobin	10.42.4	10.73.0	0.97 (0.88-1.06)	–

treatment for elevated triglycerides, (iii) serum HDL cholesterol <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL-C, and (iv) blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure

STATISTICAL ANALYSIS

Most characteristics of cases and controls were described with numbers and percentages. Other characteristics of cases and controls (e.g., age, triglyceride level, HDL cholesterol level, body mass

Table 2. Association of diabetes treatment and first diagnosis melioidosis

History of Diabetes Treatment	Case Patients	Control Patients	Adjusted Odds Ratio (95% CI)
Glyburide	23 (37.1)	99 (27.6)	1.00 (0.48-2.11)
Other sulfonylureas	14 (22.6)	76 (21.2)	1.12 (0.49-2.55)
Metformin	37 (59.7)	150 (41.8)	0.57 (0.30-1.07)
Insulin	13 (21.0)	132 (22.1)	1.67 (0.74-3.76)

index, hemoglobin level) were described with median and interquartile range or mean and standard deviation. We used binary logistic regression analysis to estimate crude odds ratio (COR) and adjusted odds ratio (AOR) and corresponding 95% confidence intervals (CI) for the association between glyburide use and the risk of melioidosis, the diagnosis of melioidosis and glyburide use being the dependent variable and the main independent variable, respectively. Logistic regression models were adjusted for the confounders listed above. Subgroup analysis was also performed regarding first diagnosis melioidosis, sex, age, glyburide density exposure, presence or absence of chronic kidney disease, presence or absence of anemia. P values of less than 0.05 for associations were considered to indicate statistical significance.

RESULTS

PATIENTS' CHARACTERISTICS

In the present study, initially, 470 diagnosed with melioidosis and type 2 diabetes were screened for the inclusion as case patients (Figure 1). However, only 146 were confirmed with positive for B. pseudomallei culture. Forty case patients were excluded due to unknown data of glyburide use. For control, 424 patients that matched for sex and age were included. One hundred and three of cases and controls were later excluded due to their diagnosis as the first episode of diabetes which indicated the co-existing findings rather than the potential risk factor. In total, there were 427 patients included in the analysis; 68 case patients and 359 control patients. Mostly there were male 50 (73.5%) for case and 260 (72.4%) for control. The medians of age were similar in both groups. But case patients were more likely to have lower body mass index (Table 1).

MAIN ANALYSIS

Twenty-five (36.8%) patients with melioidosis were current users of glyburide; among controls, the proportion of current user was 99 of 359 (27.6%) resulting in COR of 1.53 (95% CI, 0.89 to 2.63) (Table 1). For the other, insulin use, chronic kidney disease, hypertension and body mass index were also associated with lower risk of melioidosis (COR, 0.49; 95% CI, 0.26 to 0.90, COR, 0.20; 95% CI, 0.08-0.51, COR, 0.29; 95% CI, 0.17 to 0.52, COR, 0.84 ; 95% CI, 0.74 to 0.94, respectively). But in logistic regression analysis adjusted for sex, age, antidiabetic drugs, and hypertension, only hypertension was associated with lower risk of melioidosis (AOR, 0.30; 95% CI, 0.17-0.53) (Table

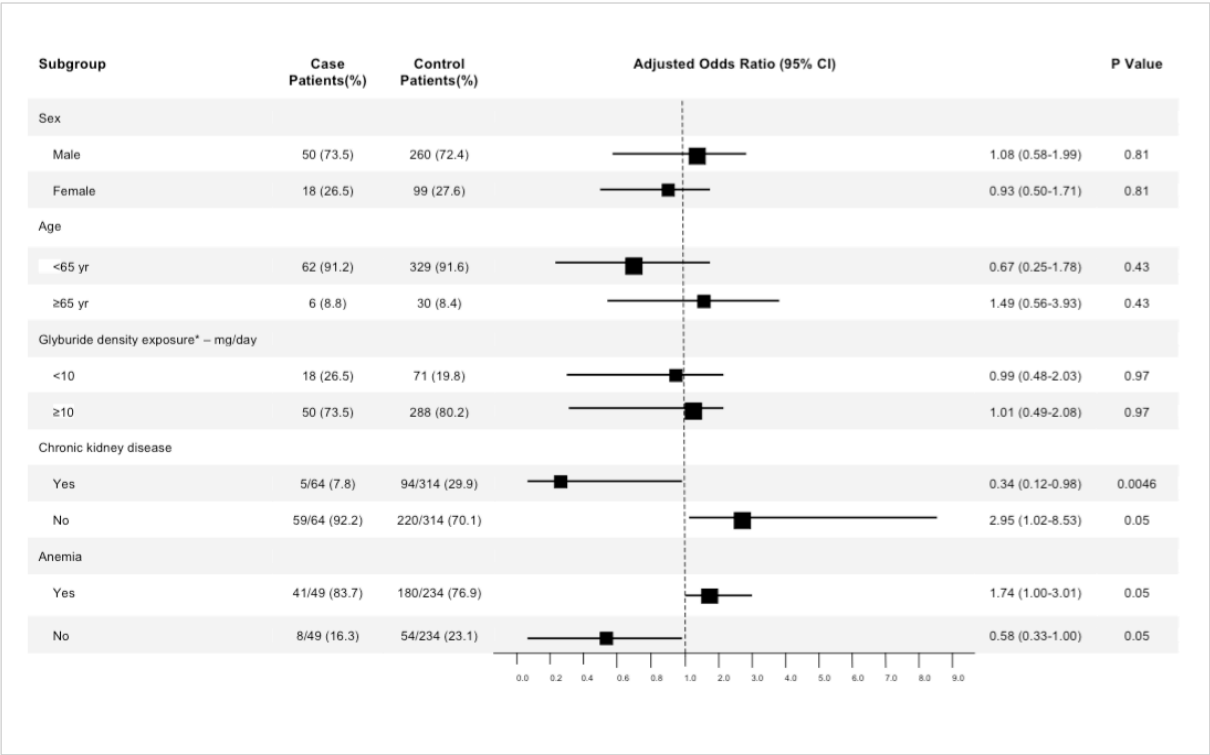


Figure 2. Adjusted odds ratio, according to the subgroup and prescribed daily dose

1). In subgroup analysis, we found no significant association between first diagnosis melioidosis and glyburide, other sulfonylureas, metformin, and insulin (Table 2). We also found that chronic kidney disease was significantly associated with lower risk melioidosis. (Figure 2.)

DISCUSSION

PRINCIPAL FINDINGS

In the present study, the association between glyburide and risk for developing melioidosis was not found. Further adjustment of confounders including age, sex, other antidiabetic drugs, and hypertension did not meaningfully alter the result. For other sulfonylureas, metformin and insulin, we did not find the association with risk for developing melioidosis as well.

COMPARISON WITH OTHER STUDIES

We did not find the association between other underlying diseases (such as nephrolithiasis, and chronic liver disease) that are known as risk factors for melioidosis according to our prior studies6,[11,23]. Moreover, we found that chronic kidney disease was significantly associated with lower risk of melioidosis that was different from the other studies.[11,18,21] One of the possible explanation for the discrepancy is the difference in methods and criteria used for the diagnosis of

chronic kidney disease. These incongruent results may be caused by the smaller sample size and a lot of missing data for diagnosis these comorbidities that made the accuracy of our results slightly low. Other findings we found that male sex and age more than 45 years were predominant in case patients that congruent to the study (Cheng AC et al, 2005) but we did not find the association of these factors due to the control patients were matched by these factors.

STRENGTH AND LIMITATION

The strength of this study is the method of selecting case by using the culture confirmation that makes sure all of case patients were truly infected by B. pseudomallei. However, the present study also has several limitations. Firstly, most of melioidosis patients had been diagnosed by other evidences of melioidosis infection such as serological diagnosis thus we had to exclude them that made our sample size slightly small. Secondly, people who had missed the information of diabetic treatment prior to admission were not included as they could not be ascertained for exposure status. Thirdly, we did not have the data for the dose-time exposure due to many of patients received diabetes prescription from primary and secondary hospitals. From this reason, we can review only the last diabetes prescription prior to admission.

CONCLUSION AND IMPLICATION

Overall, the risk of melioidosis among type 2 diabetic patients was not found to be associated with glyburide. Therefore, the further studies with larger sample size for more accurate estimation of the association between glyburide use and risk of melioidosis in type 2 diabetes is suggested.

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