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Relationship of metformin with the risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis.

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Abstract

Aims: This study is to systematically investigate the relationship between metformin and risk of pancreatic cancer in patients with type 2 diabetes mellitus.
Methods: A systematic literature search was performed on PubMed, Embase, Cochrane Library, Highwire, CBM, CNKI, Wanfang, VIP databases. Cohort or case control studies of metformin and risk of pancreatic cancer in patients with type 2 diabetes mellitus were included. The Newcastle-Ottaua Scale score was used for quality evaluation and meta-analysis was performed using RevMan5.2 Meta-analysis software.
Results: Nine studies were included in this study. The results showed that the risk of pancreatic cancer was significantly reduced in metformin treatment group (RR=0.61, 95% CI (0.55, 0.67), P<0.001). Subgroup analysis showed that patients with type 2 diabetes in treatment with metformin and sulfonylurea (RR=0.57, 95% CI (0.51, 0.64),P<0.001) or insulin (RR=0.61, 95% CI (0.53, 0.70), P<0.001) could reduce the risk of pancreatic cancer.
Conclusions: Metformin treatment reduces the risk of pancreatic cancer in patients with type 2 diabetes.

Keywords: Pancreatic cancer, Metformin, Diabetes mellitus, Type 2, Meta-analysis.

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Introduction

Pancreatic cancer mainly refers to pancreatic exocrine adenocarcinoma that has the characteristics of high malignancy, rapid development, and poor prognosis [1]. In the United States, 43,920 pancreatic cancer patients are diagnosed each year, resulting in approximately 37,390 deaths [2]. Pancreatic cancer is the fourth most common cause of cancer death worldwide [1,3]. Radical surgery is one of the treatment methods for pancreatic cancer [4]. However, early diagnosis is difficult with low general surgical resection rate from 10% to 30% [4]. Chemotherapy may improve the quality of life but not the long-term survival [5]. Radiotherapy can relieve the pain, but not other symptoms [6]. Smoking, excessive drinking, chronic pancreatitis and family history of cancer are widely recognized as potential risk factors for pancreatic cancer [7]. In addition, epidemiological studies have shown that diabetes, especially non-insulin-dependent diabetes mellitus (Type 2 Diabetes, T2DM) can increase the risk of pancreatic cancer [2,8,9]. In recent years, the incidence of pancreatic cancer in T2DM patients significantly increased, and the prognosis is poor in most patients because of difficulty in early diagnosis, high degree of malignancy, rapid development and lack of treatment with 5-year survival rate of less than 5% [10].

Therefore, it is of great importance to develop the potential drugs for the prevention and treatment of pancreatic cancer in T2DM patients. Metformin is one of the recommended first-line drugs in the treatment of T2DM. Its effects are acted mainly through reducing insulin resistance, improving the hypoglycemic effect by insulin and reducing blood sugar in T2DM patients [11]. It has been found that metformin may not only lower blood glucose in T2DM, but also significantly reduce the malignancy rates, including pancreatic cancer, lung cancer, esophageal cancer, colon cancer, liver cancer, and breast cancer [12-14]. Two studies in the United States have shown that metformin significantly reduced the risk of pancreatic cancer in T2DM patients treated with metformin compared with those without [15,16]. It is reported [17] that metformin inhibited the growth of pancreatic cancer cells by down-regulating the activity of insulin-like growth factor 1 signaling pathway. It is also shown [18] that metformin inhibited the activity of respiratory chain complex I to reduce the synthesis of ATP, thereby increasing AMP/ATP ratio, activating of AMPK pathway, and the DNA synthesis and inhibiting cell proliferation of pancreatic cancer cell. Lee et al. [19,20] showed that there were no differences between metformin and other hypoglycemic drugs in reducing the

incidence of pancreatic cancer. However, many epidemiological studies [21,22] have shown the role of metformin in the prevention of pancreatic cancer. Therefore, whether metformin can reduce the risk of pancreatic cancer is still controversial.

In this meta-analysis, the relationship between metformin and pancreatic cancer in T2DM patients was investigated. Our findings may provide reliable evidence for further clinical prevention and treatment of pancreatic cancer in T2DM patients.

Materials and Methods

Inclusion and exclusion criteria

We included studies that met the following criteria: 1) published studies on the relationship between metformin and pancreatic cancer in T2DM patients; 2) similar study aims and statistical methods with complete data; and 3) cohort study or case-control study. In the cohort study, the metformin group was treated with metformin, and the control group was treated with other antidiabetic drugs (including sulfonylureas, thiazolidinediones, or insulin). In the case-control study, case group were T2DM patients with pancreatic cancer, control group were T2DM patients without pancreatic cancer, and exposure was metformin.

We excluded studies that met the following criteria: 1) flawed study design flaws with incomplete data; 2) exposure factors were not metformin; 3) no evaluation of relationship between metformin and pancreatic cancer; or 4) duplicates.

Search strategy

The terms, including "metformin", "biguanides", "antidiabetic", "diahetes", "diahetes mellitus", "abnormal glucose metabolism", "hyperglycemia", "pancreatic cancer", "pancreatic tumor", "pancreatic adenocarcinoma", "case-control study", "risk", "incidence" and "prevalence", were searched on PubMed, Embase, Cochrane Library, Highwire, China Biology Medicine (CBM), China Knowledge Resource Integrated Database (CNKI), Wanfang and VIP Journal Integration Platform, until September 2016. Search strategy of combined text and MeSH terms was performed depending on the requirement of databases. Clinical trials register websites and references of review papers were also reviewed for comprehensiveness.

Information extraction and evaluation

All articles were reviewed by two reviewers to independently screen titles and abstracts, and review the full-text of the eligible articles. Two reviewers extracted and compared information of all included articles, and evaluated their quality. When they disagreed with each other, disagreements were either discussed to reach a consensus between the two reviewers or decided by a third reviewer.

The extracted information included: first author, time of publication, type of study, exposure factors (use of metformin), Relative Risk (RR) and 95% Confidence Interval (CI), confounders, follow-up time. The corresponding authors were contacted by telephone or mails to provide supplemental information when essential data was lacking.

Studies were evaluated for methodological quality based on Newcastle-Ottawa Scale (NOS) score [23] in terms of selection of case and controls, comparability of cases and controls and ascertainment of exposure. The evaluations were performed by the two independent reviewers, and ≥ 7 points were considered as high-quality literature with the highest score of 9 points.

Statistical analysis

Meta-analysis was performed using RevMan5.2 (Cochrane Collaboration) [24]. Quantitative data used relative risk (RR) for efficacy analysis and categorical data used Weight Mean Difference (WMD), presented as 95% Confidence Interval (CI). χ^2 test was used for heterogeneity analysis, and heterogeneity was assessed by I^2. If P>0.1 and I^2<50%, the fixed effects model was used; otherwise, the heterogeneity was assessed to determine whether random effects model can be used. If there was obvious statistical heterogeneity but clinical homogeneity among all studies or subgroups, random effect model was used. Sensitivity analysis was performed for each outcome. A funnel plot was used to detect the presence of publication bias.

Results

Characteristics of patients

A total of 425 references were reviewed, and 9 studies were finally included after reviewing abstracts, inclusion and exclusion criteria. Seven of them [20,25-30] were cohort studies and two were [31,32] case-control studies. The characteristics of all included study were shown in Table 1, and the diagram of literature screening was shown in Figure 1.

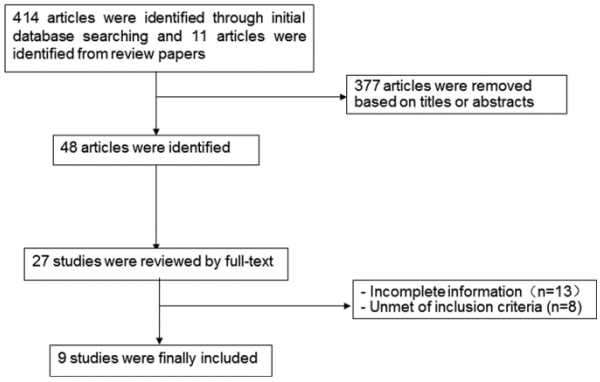

Figure 1. Flow chart of study selection process.

Quality evaluation

NOS score was used to evaluate the quality of all studies. As shown in Table 2, the NOS score suggested that the included studies were of high quality.

Comparison of metformin and non-metformin drugs

The effects of metformin and non-metformin drugs on pancreatic cancer were compared. The comparisons were performed in nine clinical studies with mild statistical heterogeneity (I^2=31%) among studies, therefore, fixed-effect model was used. It showed that the adjusted RR was 0.61 (95% CI (0.55, 0.67), P<0.001) for T2DM patients with metformin compared with those without, as in Figure 2. When 2 case-control studies were excluded, the revised RR was 0.62 (95% CI (0.56, 0.680, P<0.001) for T2DM patients with metformin compared with those without. This result indicates metformin has better protection effect than non-metformin drugs on pancreatic cancer.

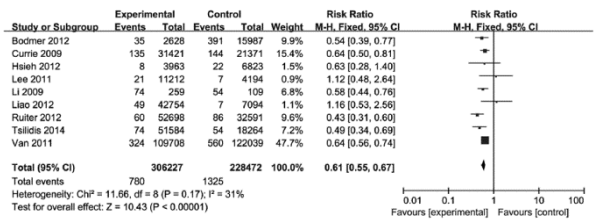

Figure 2. *Comparisons of metformin and non-metformin in the treatment of pancreatic cancer in patients with type 2 diabetes mellitus by meta-analysis.*

Comparison of metformin and sulfonylurea drugs

The effects of metformin and sulfonylurea drugs on pancreatic cancer were also compared. The comparisons were performed in 6 clinical studies with no statistical heterogeneity (I^2=0), therefore, fixed-effect model was used. It showed that the adjusted RR was 0.57 (95% CI (0.51, 0.640, P<0.001) for T2DM patients with metformin compared with those with sulfonylurea drugs, as in Figure 3. When case-control studies were excluded, the revised RR was 0.58 (95% CI (0.52, 0.65), P<0.001) for T2DM patients with metformin compared with those with sulfonylurea drugs, indicating that the protection effect of metformin on pancreatic cancer is better than sulfonylurea drugs.

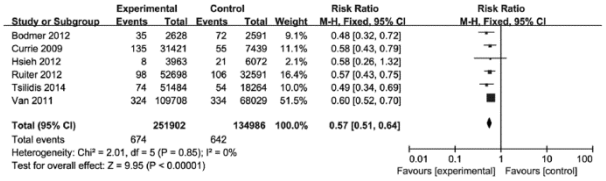

Figure 3. *Comparisons of metformin and sulfonylurea drugs in the treatment of pancreatic cancer in patients with type 2 diabetes mellitus by meta-analysis.*

Comparison of metformin and insulin

Furthermore, the differences in protection effect on pancreatic cancer between metformin and insulin were compared. The comparisons were performed in 5 clinical studies with no statistical heterogeneity (I^2=0), therefore, fixed-effect model was used. It showed that the adjusted RR was 0.61 (95% CI (0.53, 0.70), P<0.001) for T2DM patients with metformin compared with those with insulin, as in Figure 4. When case-control studies were excluded, the revised RR was 0.59 (95% CI (0.50, 0.70), P<0.001) for T2DM patients with metformin compared with those with insulin. This data suggests the protection effect of metformin.

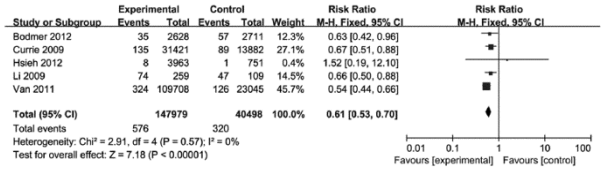

Figure 4. *Comparisons of metformin and insulin in the treatment of pancreatic cancer in patients with type 2 diabetes mellitus by meta-analysis.*

Table 1. *Baseline characteristics of included studies.*

Studies	Study design	Country of study	Number of patients (T/C)	Age (years)	Length of follow up	Control group	Calibration parameters
Li [11]	Case-control	United States	973 /863	61	NR	Insulin	Age, sex, race, smoking, drinking, body mass index, family history of cancer
Currie [12]	Cohort	United Kingdom	31421 /17506	62	2.42	Sulfonylurea drugs; insulin	Age, sex, smoking, history of malignancy
Lee [13]	Cohort	United Kingdom	11309 /22948	≥ 20	3.52	Non-metformin	Age, gender, other oral anti-diabetic agents, CCI score, duration of metformin exposure
Van [14]	Cohort	United Kingdom	109708/ 122403	63	9	Non-metformin	Age, gender, body mass index, smoking, glycosylated haemoglobin, hospitalization 1 year prior to follow-up, acute coronary syndrome, hypertension, hyperlipidemia, stroke
Hsieh [15]	Cohort	Taiwan	61777 /677378	61.4	8	Sulfonylurea drugs; insulin	Age, gender

Bodmer [16]	Case-control	United States	2763 /16578	69.5	Not applicable	Non-metformin	Age, sex, BMI, smoking, alcohol consumption, diabetes duration
Liao [17]	Cohort	United States	49803 /199212	55.9	6.3	Sulfonylurea drugs; insulin	Chronic pancreatitis, age, gallstones, hepatitis B
Ruiter [18]	Cohort	Taiwan	52698/32591	≥ 18	2.8 - 4.6	Sulfonylurea drugs	Age, sex, duration of hyperglycemia, use of other drugs, hospitalization before follow-up, dosage
Tsilidis [19]	Cohort	Netherlands	51484/18264	35 - 90	5.1	Sulfonylurea drugs	Age, sex, body mass index, smoking, drinking, use of nonsteroidal anti-inflammatory drugs, statins and hormone drugs

T: Treatment; C: Control; NR: Not Report; CCI: Complications of Composite Index.

Table 2. *Risk assessment for included studies.*

Included studies	1	2	3	4	5A	5B	6	7	8	NOS score
Li [11]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Currie [12]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Lee [13]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Van [14]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Hsieh [15]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Bodmer [16]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Liao [17]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ruiter [18]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Tsilidis [19]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

1. Representativeness of the cohort; 2. Control from the same cohort; 3. Quality of exposures; 4. Occurrence of end-point events; 5A. Control of age; 5B. Control of other confounders; 6. Quality of end-point events; 7. Length of follow-up; 8. Definition of cohort.

Discussion

The 2012 China Cancer Registration Annual Report showed that pancreatic cancer has been ranked ninth in the incidence of all malignant tumors in China with incidence rate of 8.19/10 million [33]. American Cancer Society shows that [34] the number of pancreatic cancer deaths per year is about 34,000, and 5-year survival rate is only 33%. Currently, pancreatic cancer has become one of the malignant tumors with highest mortality in China [35].

Epidemiological studies have shown that T2DM can increase the risk of pancreatic cancer [21,22,32]. For example, Ben et al showed that the risk of pancreatic cancer was 1.94 times higher in T2DM patients compared with those without (RR: 1.94, 95% CI (1.66, 2.27)) [8]. Batty [36] showed in a large cohort study that fasting hyperglycemia may increase the incidence of pancreatic cancer and associated mortality. Epidemiologic studies showed that metformin may reduce the incidence of pancreatic cancer in diabetic patients [25,31]. Metformin as an insulin sensitizer can inhibit gluconeogenesis and glycogen breakdown, promote muscle glucose uptake, and effectively reduce blood glucose [37]. Studies [38,39] have also shown that metformin can inhibit the proliferation of pancreatic cancer cells through AMPK/mTOR axis, insulin/insulin-like growth factor signaling pathway, and induction of cell cycle arrest [23].

This study showed that Metformin could effectively reduce the risk of pancreatic cancer in patients with diabetes when compared with sulfonylureas, insulin and other non-metformin drugs from analysis of nine high-quality clinical studies. Metformin was associated with a 61%, 57% and 61% decrease in risk compared with non-metformin, sulfonylureas and insulin. The sensitivity analysis showed that the results were stable. In a meta-analysis, Wang et al. [40] showed that metformin may reduce the risk of pancreatic cancer in T2DM patients. However, the meta-analysis was limited in that 1) it included both cohort study and case-control study with completely different data extracted from the treatment and control group; 2) two studies (Currie et al. [25] and Little et al. [41]) reported no data for RR calculation; and 3) incomplete literature review with low NOS score after 2012. Yu et al. [42] showed that metformin reduced the risk of pancreatic cancer by 51% and 53%, respectively, compared with sulfonylurea and insulin group; however there were no analysis of case-control studies. In a meta-analysis of relationship between metformin use and cancer [43], it showed that metformin may reduce the incidence and mortality of multiple malignancies, including liver, pancreas, colon and lung cancers. The reduction in incidence and mortality of pancreatic cancer was

most obvious (normalized relative risk of incidence SRR=0.54, 95% CI 90.35, 0. 830; mortality SRR=0.64, 95, 95% CI (0.48, 0.86)). However, in their study, subgroup comparisons with other specific hypoglycemic agents were not analysed. Sadeghi et al. [44] showed that the use of metformin was associated with an increased survival rate in T2DM patients with pancreatic cancer. Consistently, we found that metformin had protection effects on pancreatic cancer in T2DM patients. Furthermore, the literatures included in this paper were of high quality and published in the near 10 years with NOS score of 7 to 9 points, indicating the robustness of the conclusions.

However, there are still some limitations in this study. Only a few cohort studies were included, and some of the literature did not provide detailed information on age, gender, dosage of metformin and other hypoglycemic agents, and length of use. Therefore, the above calibration parameters cannot be excluded. In addition, most of the included studies were in English language, indicating language bias. Calibration parameters including smoking, alcohol, race, region, and pancreatic cancer lesions were not analysed, introducing potential bias of this study. Last but not least, clinical randomized controlled trials were not identified.

In conclusion, this study analysed 9 high quality studies and showed metformin treatment reduced the risk of pancreatic cancer in patients with type 2 diabetes, when compared with sulfonylurea or insulin. Our findings may shed light on the treatment of pancreatic cancer in patients with type 2 diabetes.

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Conflict of Interest

The authors declare no conflict of interests.

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