

Pancreatic Carcinoma: Exploring its Relationship with Diabetes and the Potential Chemopreventive Effects of Metformin

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Abstract

Background: Pancreatic cancer and type 2 diabetes mellitus have been found to be interrelated, with emerging evidence suggesting that metformin may have a chemoprotective role in reducing the risk of pancreatic cancer in patients with diabetes. **Methods:** A comprehensive systematic search was conducted across databases, including PubMed, Web of Science, and the Cochrane Library. The search terms included “metformin,” “biguanide,” “pancreatic cancer,” “pancreatic tumor,” and “diabetes mellitus” in the title and abstract fields. **Results:** A meta-analysis of 18 studies using a random-effects model showed that metformin use was associated with a reduced risk of pancreatic cancer in patients with type 2 diabetes, compared to those who did not use metformin. **Conclusion:** This review highlights the chemoprotective effect of metformin in reducing the risk of pancreatic cancer among diabetic patients. Further research is needed to explore the mechanisms behind this association and to confirm these findings.

Keywords: Pancreas cancer- diabetes mellitus- metformin

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Introduction

Pancreatic cancer ranks 14th in the global cancer incidence rate and 7th in the global cancer mortality according to GLOBOCAN 2020 statistics [1]. Pancreatic cancer is highly malignant in nature and high incidence of mortality with 495,733 new cases of pancreatic cancer are diagnosed each year worldwide and 466,003 deaths [1]. Surgery is the main modality of treatment for carcinoma Pancreas patients with 5 years survival rate of 15% to 25% [2]. Pancreatic cancer is the cause of high rate of mortality. Type 2 Diabetes mellitus is another leading cause of significant morbidity and mortality owing to a global increase in its incidence. Over 1 million deaths per year can be attributed to diabetes alone, making it the ninth leading cause of mortality. Its prevalence is predicted to reach up to 700 million by 2045 [3]. It is projected that by 2045, the prevalence of T2 Type2 Diabetes mellitus could reach as high as 700 million individuals. While long-standing diabetes has been associated with a relatively modest risk for pancreatic cancer (Pancreatic cancer), the emergence of new-onset diabetes mellitus

(NOD), particularly after the age of 50, is frequently seen as an early warning sign of an underlying pancreatic cancer [4].

Early identification of risk factors of carcinoma Pancreas i.e. smoking, drinking, obesity, diabetes, pancreatitis, and pancreatic cancer family history and early interventions to prevent these risk factors and in high risk individuals helps in reducing incidence and mortality of this deadly cancer [5]. Pancreatic cancer and diabetes mellitus have been subjects of significant research interest due to their complex relationship. While there is still some disagreement on the precise link between the duration of diabetes and the risk of pancreatic cancer, numerous studies have consistently shown that the risk of developing pancreatic cancer is notably higher in patients with diabetes [6]. Given the context provided, our objective is to conduct a comprehensive literature review to understand the intricate and multifaceted connection between diabetes and pancreatic cancer (Pancreatic cancer).

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Metformin, as a first-line drug for type 2 diabetes mellitus, has garnered considerable attention due to its potential role in reducing mortality in patients with pancreatic cancer. Several studies have indicated that patients with pancreatic cancer who were treated with metformin experienced a significant improvement in overall survival period and 5-year survival rates when compared to those who received other antidiabetic drugs or did not use metformin at all [7].

The goal of this review article is to provide a more detailed and rigorous investigation into the connection between the use of metformin in diabetes patients and the incidence rate of pancreatic cancer. By analyzing the collective evidence from various studies, the researchers hope to shed further light on the potential impact of metformin in pancreatic cancer development among individuals with diabetes. This research could have implications for clinical practice and possibly contribute to better management and prevention strategies for pancreatic cancer in diabetic patients. Given the context provided, our objective is to conduct a comprehensive literature review to understand the intricate and multifaceted connection between diabetes and Pancreatic cancer.

Materials and Methods

This paper is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). An electronic search on PubMed, Web of Science, Cochrane Library, databases, using the keywords “metformin” OR “biguanide” AND “pancreatic cancer” OR “pancreatic tumor” in “Title/ Abstract” AND “diabetes mellitus” was done.

Inclusion criteria

We took only case-control or cohort study of 10 year period between 2013 to 2023 were taken for review. Reporting or including studies on the association between metformin use and pancreatic cancer risk; reporting the Relative Risk (RR), Hazard Ratio (HR) or Odds Ratio (OR) and 95% confidence interval (CI) of pancreatic cancer, or providing data that we can calculate them. Only those articles which were original research article for which free full text was available were taken. Studies those were in english language were only taken up for review.

Exclusion criteria

Cross-sectional studies; duplicated studies; preclinical studies (such as in vivo studies, primary studies, and animal studies); abstracts, case reports, reviews, conferences, letters, and books; only showing the relationship between metformin and pancreatic cancer mortality were excluded. Studies lacking necessary data. Studies with language other than english were excluded. Studies without free access were excluded.

Results

After thorough research via electronic search total 1275 articles were obtained by preliminary search. Only

114 articles were selected after reading title and abstract. Out of them only 17 article were taken up for review after reading the full text and were consistent with our search (Table 1). Out of them two were prospective studies. Twelve were retrospective studies and four were case control studies. Eight studies showed protective benefit of metformin for Pancreatic cancer.i.e. study by Amin et al.2017, [8] Yang et al.2022, [9] Cheon et al. 2014, [10] Choi et al.2016, [11] Lee et al. 2018, [12] Lin et al. 2015, [13] You et al.2020, [14] Lu et al.2015 [15]. All the studies that were chosen presented findings regarding the connection between metformin usage and the likelihood of developing pancreatic cancer. However, it's worth noting that the comparison drugs used as reference points in these studies were not the same. Eight studies showed p value for metformin not statistically significant for improved survival in diabetic patient with pancreatic cancer.i.e study by Ambe et al. 2016, [16] Chaiteerakij et al. 2016, [17] De Jong et al.2017, [18] Farmer et al.2019, [19] Frouws et al.2016, [20] Hwang et al. 2013, [21] Walker et al.2014, [22] Wang et al.2013 [21]. One studies showed use of metformin is associated with increase risk of Pancreatic cancer in diabetic patients.i.e Oh et al.2020 [23].

Overall analysis

An overall analysis of 17 articles by use of random effect model showed that compared with no use of metformin, the use of metformin could reduce the risk of pancreatic cancer in patients with type 2 diabetes.

Discussion

Pancreatic cancer is associated with poor prognosis. Type2 Diabetes mellitus is known as the most common risk factor of Pancreatic cancer. A meta-analysis by Ling et al. [24] suggested an increased Pancreatic cancer related mortality with T2 Type2 Diabetes mellitus (relative risk [RR] 1.67; [95%CI: 1.30-2.14]) [8]. Obesity and smoking are two most common independent factors associated with Pancreas cancer even after adjusting these two factors which are independently most common factors of Pancreatic cancer still Type2 Type2 Diabetes mellitus is an important risk factor of Pancreas cancer. Mendelian randomization studies examining the potential link between long-standing type 2 diabetes and pancreatic cancer have produced mixed results [25]. While some studies suggest a connection, others do not. A pooled analysis of these studies by Yuan et al. found a modestly increased risk of pancreatic cancer in long-standing diabetes patients, but more research is needed to confirm this association [26].

Biomarkers play a crucial role in early diagnosis of Pancreatic cancer among Type2 Diabetes mellitus patients. A study found that patients with pancreatic cancer and diabetes mellitus (DM) exhibited elevated levels of glucagon when stimulated by glucose, implying that glucagon could serve as a potential biomarker [27]. Murakami et al. suggested that a serum CA19-9 level cutoff of 75 U/mL can effectively differentiate between individuals with diabetes with or without pancreatic

Table 1. Results of Various Studies Taken for Review

| First author name, year | Study design | No.of cases | No. Of controls | Study period | Results |
|-------------------------------|----------------------------|-------------|-----------------|--------------|--|
| Ambe et al. 2016 [16] | Prospective study | 19 | 25 | 1986-2013 | Metformin use was associated with improved survival outcomes in patients with resected pancreatic cancer, but the difference was not statistically significant p=0.3875. |
| Amin et al. 2017 [8] | Prospective study | 1098 | 818 | 2007-2011 | Diabetic patient on metformin at time of pancreatic cancer diagnosis have improved survival P<0.01 |
| Chaiteerakij et al. 2016 [17] | Retrospective study | 366 | 614 | 2000-2011 | Hazard ratio was 0.93 at 95% CI metformin was not statistically significant for improved survival in diabetic patient with pancreatic cancer p=0.28 |
| Yang et al.2022 [9] | Retrospective cohort study | 76 | 92 | 2012-2020 | Metformin use was associated with improved survival outcomes in patients with stage I and II pancreatic Cancer H.R -0.47 at 95%CI but not in advanced stage. |
| Cheon et al. 2014 [10] | Retrospective cohort study | 65 | 62 | 2005-2011 | Metformin use was associated with improved survival outcomes in patients. p=0.058 |
| Choi et al. 2016 [11] | Retrospective cohort study | 56 | 127 | 2003-2010 | Patient with advanced pancreas Cancer receiving metformin along with chemotherapy is associated with longer overall survival p=0.044 |
| De Jong et al. 2017 [18] | Cohort | 37,215 | 19,899 | 1998-2011 | Use of metformin does not decrease risk of gastrointestinal Cancers H.R. =0.97 at 95% C.I |
| Farmer et al. 2019 [19] | Cohort | 6105 | 49,524 | 1990-2014 | No protective effect of metformin on individual outcome H.R=1.02 at 95% CI |
| Frouws et al. 2016 [20] | Retrospective cohort study | 77 | 830 | 1998-2011 | No association was found between overall survival, pancreatic cancer, and metformin use. p=0.26 |
| Hwang et al. 2013 [21] | Retrospective cohort study | 247 | 269 | 2003-2010 | Metformin use is not associated with improved survival in subjects with advanced PAC. p=0.367 |
| Lee et al. 2018 [12] | Retrospective cohort study | 6,88,656 | 2,77,797 | 2009-2012 | Diabetic patient are two fold increase risk of PAC when compared to non diabetic patient. Metformin use in diabetes decrease risk of PAC O.R=0.86 |
| Lin et al. 2015 [13] | Cohort | 36270 | 145080 | 2005-2010 | Anti-diabetic therapy (ADT) especially metformin and long acting insulin protect against pancreas cancer H.R=0 at 95%C.I |
| Walker et al. 2014 [22] | Case control | 81 | 89 | 2006-2011 | Metformin use is not associated with decrease in risk of PAC in DM2 and does not alter the association between DM2 and Pancreatic cancer risk. |
| Wang et al. 2013 [23] | Case control | 2158 | 8609 | 1998-2009 | Metformin use is not associated with decrease in risk of PAC. O.R= 1.14 For metformin users with pancreatic cancer |
| You et al.2020 [14] | Cohort | 1,31,877 | 1,31,877 | 2005-2014 | Metformin was associated with risk reduction in stomach, colon and liver as well as pancreatic cancer in DM2 patient |
| Lu et al. 2015 [15] | Case control | 175 | 856 | 1996-2010 | New onset diabetes or elevated HBA1C level associated with increase risk of pancreatic cancer.The relation between different anti-diabetic medications and pancreatic cancer seems to vary in strength, with the highest risk among users of insulin |
| Oh et al. 2020 [23] | Cohort | 19,546 | 19,546 | 2011-2015 | Metformin increase risk of PC O.R=0.88 |

cancer (Pancreatic cancer). At this specified threshold, the CA19-9 test exhibited a sensitivity of 69.5% and specificity of 98.2% for detecting Pancreatic cancer, with an area under the curve (AUC) of 0.875 (95% confidence interval: 0.826-0.924) [28]. Thrombospondin-1 (TSP-1) is another important biomarker is seen elevated in patient

with T2 Type2 Diabetes mellitus Pancreatic cancer and is not seen in long-standing T2DM [29].

Pancreatectomy is the first line of management of Pancreas cancer and is preferred modality for early stage. But long standing uncontrolled T2 Type2 Diabetes mellitus is non to delay wound healing and hence increases

risk of post operative complications. According to a review conducted in 2013, individuals with diabetes exhibited an elevated risk of experiencing post-operative complications, with a rate of 45% compared to 35% in non-diabetic patients [30]. A study by Ambe et al. done in 2016 suggested that Metformin use was associated with improved survival outcomes in patients with resected pancreatic cancer, but the difference was not statistically significant [16].

Additionally, it was observed that having a baseline HbA1c level exceeding 6.5%-7.0% was linked to reduced survival rates [31]. A study by Amin et al. 2017 suggested that Diabetic patient on metformin at time of pancreatic cancer diagnosis have improved survival thus supporting the above stated statement [8].

Studies investigating the influence of diabetes on Pancreatic cancer (Pancreatic cancer) patients undergoing chemotherapy have indicated that pre-existing diabetes may be linked to an increased risk of mortality. Kleef et al. observed a higher mortality rate among diabetes patients receiving adjuvant chemotherapy, with a hazard ratio (HR) of 1.19 (95% confidence interval: 1.01-1.40) [32]. Likewise, Hank et al. reported that the median overall survival in diabetes patients who received neo-adjuvant chemotherapy was shorter compared to non-diabetic patients (18 months vs. 54 months) [33]. Mechanism behind poor outcome is not clear some studies suggest that change in tumor microenvironment resulting in increase risk of metastasis by tumor hypoxia and perineural invasion [34]

Various drug are available and prescribed for T2 Type2 Diabetes mellitus in our review we will be focused on use of metformin. Metformin has attracted significant attention due to its potential anti-cancer effects i.e chemo-protective role in the context of Pancreatic cancer. Metformin is the primary drug of choice for managing Type 2 Diabetes (T2DM), and numerous studies have explored its impact on three crucial aspects related to Pancreas cancer. 1: Assessing Metformin as a factor that modifies the risk of developing Pancreatic cancer in individuals with T2 Type2 Diabetes mellitus [35]. Investigating the influence of Metformin on overall survival rates after Pancreatic cancer therapy [36]. Evaluating Metformin's role as an adjuvant therapy for individuals already diagnosed with Pancreatic cancer [37]. Early-stage pancreatic cancer patients who have mild hyperglycemia along with obesity could potentially be suitable candidates to initiate treatment with metformin. To sum it up, recent well-conducted studies with enhanced statistical analysis, accounting for factors like immortal time bias, have not shown any significant risk reduction in pancreatic cancer or improvements in overall survival as a result of metformin therapy. In the future, phase 3 randomized controlled trials (RCTs) will be valuable in shedding more light on this matter, particularly in the case of carefully selected individuals with pancreatic cancer. [38].

In conclusion, in this comprehensive review, we have summarized the intricate relationship between diabetes mellitus (DM) and Pancreatic cancer. It is well-established

that long-standing diabetes is considered a significant risk factor for the development of Pancreas cancer. Early detection of Pancreatic cancer in individuals with Type 2 Diabetes mellitus is crucial but clinically challenging. Pancreatic cancer is relatively rare in both the general population and among those with diabetes. Therefore, the development of a screening strategy for the diabetic population to detect Pancreatic cancer is urgently needed.

A clinically useful and cost-effective screening tool is essential for identifying Pancreatic cancer in patients with long-standing diabetes. Additionally, various biomarkers have been identified to differentiate Pancreatic cancer-related diabetes from the more common type 2 diabetes (T2DM). Combining different clinical and biochemical parameters has led to the development of various screening tools. Effective screening and early recognition of Pancreatic cancer can significantly improve the outcomes for individuals affected by this devastating cancer.

The question arises: Can we delay the onset or halt the progression of Pancreatic cancer in patients with DM? Future research may explore strategies to improve insulin resistance, such as regular physical exercise, intermittent fasting, and low-fat diets. Implementing healthy behaviors, like smoking cessation, is also critical for patients with long-standing DM. Furthermore, the potential role of glucose-lowering medications, such as metformin, in delaying the onset of Pancreatic cancer requires further investigation through longitudinal studies.

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Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute .
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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