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Sitagliptin and Acute Pancreatitis: A Systematic Review and Meta-analysis

Hyder Osman Mirghani [a#], Salem Ahmed S. Shaman [b*$] and Ibrahim Mahmoud Hussain Aljwah [c]

[a] Internal Medicine and Endocrine, Medical Department, Faculty of Medicine, University of Tabuk, KSA, Saudi Arabia.
[b] King Khalid Hospital, Ministry of Health, Tabuk, Saudi Arabia.
[c] King Salman Armed Forces Hospital, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background and Objectives: Sitagliptin is a dipepidyl peptidase inhibitor (DPP-4i) with gentle antidiabetic effects with a lower risk of hypoglycemia. The association with acute pancreatitis is controversial. The current meta-analysis aimed to assess the relationship of sitagliptin and acute pancreatitis.
Methods: The literature in PubMed and Google Scholar was searched for relevant articles published in the last ten years up to September 2021. The keywords sitagliptins, DPP-4i, acute pancreatitis were used with the protean AND or OR. Among the 204 articles retrieved, 24 full-texts were assessed for eligibility and only five studies (Three from the USA, one from Asia, and one from Canada) met the inclusion criteria for the systematic review. The author name, year of publication, country, type of study, number of patients, and the duration of the study were reported.
Results: There were five studies**.** The total number of patients were 729808 with 6459 events. The studies showed no increased rate of acute pancreatitis following sitagliptin use, odd ratio, 0.79, 95% CI, 0.29-2.15, a significant heterogeneity was observer, I^2 for heterogeneity=98%, P-value,

[#]Associate Professor
[$]Medical Intern
**Corresponding author: E-mail: xsalem12300@gmail.com;*

<001, the P-value for overall effect was 0.65 and the chi-square, 160.15.
Interpretation and Conclusion: Sitagliptin use is not associated with acute pancreatitis.

Keywords: Acute pancreatitis; DPP-4i; sitagliptins.

1. INTRODUCTION

Sitagliptin is one of the dipeptidyl peptidase inhibitors (DPP-4i) a class of oral hypoglycemic medications with a lower propensity for hypoglycemia, moderate hypoglycemic efficacy, and weight neutral effect, the drugs are available as oral products alone or in combination with metformin or sodium-glucose co-transporters inhibitors with a large market share [1]. However, DPP-4i are blamed for many side effects including admission for heart failure with saxagliptin, and aspiration pneumonia due to the degradation of substance P [2, 3], the association of DPP-4 and acute pancreatitis is a matter of controversy [4, 5]. Acute pancreatitis is a condition where the pancreas becomes inflamed (swollen) over a short period of time. It is a morbid disease with a high rate of mortality depending on severity, it may constitute up to 3% of admission to surgery [6]. The available reviews are mostly on DPP-4i, the literature on the individual drugs and pancreatitis are scarce. Thus, we conducted this review to assess the relationship between sitagliptin and acute pancreatitis.

2. METHODS

2.1 Eligibility Criteria According to PICOS

We included retrospective, case-control studies, and randomized controlled trials published in English language and assessing sitagliptin relationship to acute pancreatitis. Animals and experimental studies, case reports, and case series were excluded. All the articles during the last ten years up to January 2020 were included.

Outcomes: The primary outcome is the development of acute pancreatitis while on sitagliptin

2.2 Information Sources and Search Methods

A systematic manual search was conducted in PubMed and Google Scholar databases during the last ten years up to September 2021. The following search terms were applied: sitagliptins, DPP-4i, acute pancreatitis were used with the protean AND or OR, the filter was set to English publications and human studies.

A total of 204 studies were identified through the database search. Only five articles stand after applying the inclusion and exclusion criteria. Titles and abstracts were screened independently by two authors and full texts retrieved for the manuscripts found relevant for the topic. Additional articles were searched and identified through hand searching of the bibliography. Any disagreement in the selection of articles and data was discussed and solved between the researchers. A data sheet was used to extract the author's names, country, type of study, study period, and the 95% confidence interval, and the significance. The quality of the studies included in the meta-analysis was assessed by Newcastle Ottawa Scale and a modified Cochrane scale [7, 8]. The different phases of the systematic review were reported in Fig. 1 and Table 1.

2.3 Statistical Analysis

We entered the dichotomous data manually in to the most recent RevMan, the outcome measures were obtained using the random effect because of the substantial heterogeneity observed. A p-value of <0.05 was considered significant.

3. RESULTS

Among these 204 papers, 24 full-text articles were assessed for eligibility: only five studies (Three published in the USA, one from Asia, and one from Canada) met the inclusion criteria for the systematic review. The total number of patients were 729808 with 6459 events. The studies showed no increased rate of acute pancreatitis following sitagliptin use, odd ratio, 0.79, 95% CI, 0.29-2.15, a significant heterogeneity was observer, I^2 for heterogeneity=98%, P-value, <001, the P-value for overall effect was 0.65 and the chi-square, 160.15 Fig. 2.

4. DISCUSSION

In the current review, Sitagliptin use is not associated with a significant risk of acute

pancreatitis, a meta-analysis on Dipeptidyl Peptidase-4 inhibitors (DPP4i) inhibitors and include 165 studies showed that DPP-4i were not associated with pancreatitis [14], further meta-analysis on incretins showed no associations [15] (odds ratio 1.08; 95 % CI [0.84-1.40]). The study was limited by including all DPP-4 and Glucagon like peptides-1 receptors agonists (GLP-1 receptor agonists). The previous observations supported the findings of Li et al meta-analysis on incretin-based therapy. However, Li and colleaguespooled all types of studies that limited their study [16]. On the other hand, Tkac et al combined three trials on Saxagliptin, alogliptin, and sitagliptin (SAVOR-TIMI 53, EXAMINE, and TECO trials respectively) and found that incretins increased the risk of acute pancreatitis when combined, despite the fact that each trial showed no increased risk. Importantly, the trial's primary outcomes were cardiovascular endpoints [17]. Further meta-analysis published in Italy in 2014 that assessed DPP-4 I and other comparators showed no differences regarding acute pancreatitis [18] supporting their previous observation published in the year 2011 [19].

4.1 Sitagliptin Effects on the Pancreas

Animal studies showed a protective effects on the beta cells of the pancreas with no detrimental effects on the exocrine cells [20], Ston et al. [21] showed similar protective effect. Further studies showed the protective effects of sitagliptin by anti-oxidative and anti-inflammatory effects [22], and a recent study on mice showed a decrease in apoptosis [23].

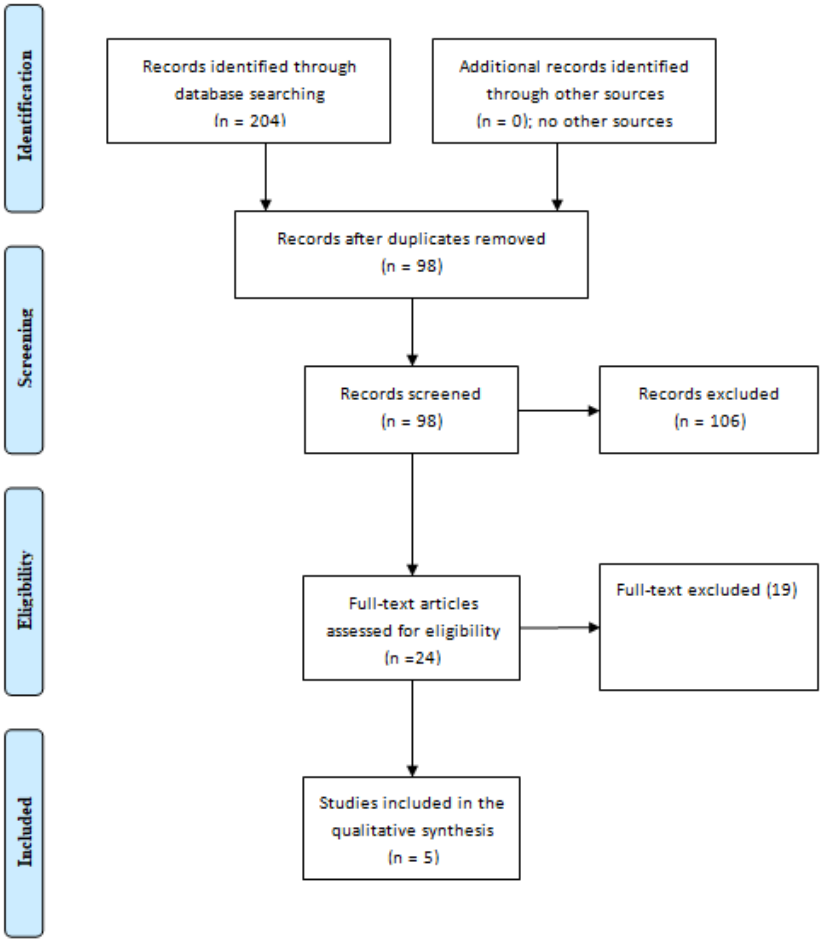

Fig. 1. The different phases of the literature search

Table 1. Sitagliptin and acute pancreatitis

Author	Year	Country	Duration	Method	intervention	Control	95%*CI*	P-value
Clements et al. [9]	2015	Canada	20w	Case-control	46/57 689	48/55 705	0.55-1.55	Not sig.
Engel et al. [10]	2010	USA	24 months	Analysis of RCT	4/4708	4/3942	−0.25, 0.03	Non sig
Grag et al. [11]	2010	USA	36 months	Retrospective	67/15826	154/38615	0.7-1.3	Non sig.
Green et al. [12]	2015	USA	36 months	RCT	23/7257	12/7266	0.95-3.88	Non sig
Tseng et al. [13]	2015	Taiwan	10 years	Retrospective	261/ 89,800	5840/ 449,000	1.40-1.81	Sig.

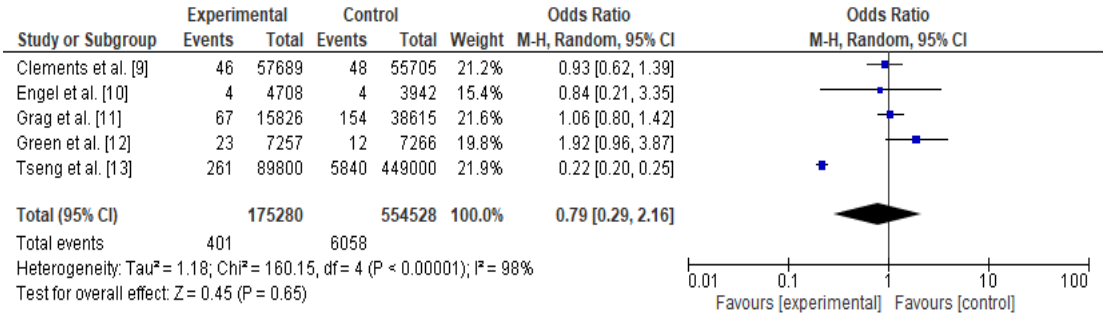

Fig. 2. The association of sitagliptin with acute pancreatitis

5. CONCLUSION

Sitagliptin use is not associated with a significant risk of acute pancreatitis

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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