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ASSOCIATION TYPE 2 DIABATES MELLITUS AND GASTRIC CANCER : THE SYSTEMATIC REVIEW

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Abstract
Gastric cancer is one of the most common types of malignant gastrointestinal tumors, and its incidence rates are climbing at an alarming rate, making it one of the most common forms. It is known as radical resection, and it is the only treatment for stomach cancer that has been demonstrated to be successful. Previous studies have established a correlation between obesity and an increased danger of acquiring cancers of the stomach and heart. Insulin resistance and the resultant hyperinsulinemia have been presented as possible causes for this syndrome. Insulin sensitivity has also been postulated. Even though obesity was not found to be directly linked to non-cardiac gastric cancer, insulin resistance may potentially play a role in the development of diabetes-related gastric cancer. This is the case despite the fact that insulin resistance may have a role in the development of diabetes-related gastric cancer. Hyperglycemia, also known as high blood sugar, can promote the growth, proliferation, invasion, and migration of cancer cells. This is especially true for cancers that affect the breast, liver, bladder, pancreas, colorectum, and endometrium. An in vitro and in vivo study discovered that it can also promote the proliferation and growth of human gastric cancer cells while also developing chemoresistance to the chemotherapeutic agent 5-fluorouracil in GCa cells. These findings were made public in the journal Cancer Research. Diabetes has been linked repeatedly to an increased likelihood of developing stomach cancer, according to research. This demonstrates the need of ensuring that the therapies used to lower the patient's blood sugar levels are carried out in the most effective manner possible.

Keyword: *Diabetes Mellitus; Gastric Cancer; Hyperglycemia; Oncogen*

INTRODUCTION

The chance of developing malignancies of the breast, liver, pancreas, colorectum, endometrial, kidney, as well as non-Hodgkin lymphoma and the urinary bladder, may be increased in people who have diabetes mellitus.[1,2] It is possible that insulin resistance, poor glycemic control, oxidative stress, and a pro-inflammatory condition are the underlying mechanisms that cause individuals with diabetes to have an increased risk of developing cancer. In addition, the use of anti-diabetic medications, the length of time that a person has had diabetes, and the severity of their diabetes status in conjunction with a variety of comorbidities may all have a role.[3]

Men and people who are at least 50 years old have a higher risk of developing gastric cancer. Important risk factors include being overweight or obese, smoking, eating a diet high in salt, and having an infection caused by Helicobacter pylori (H. pylori). The incidence of gastric cancer is low in North America and most parts of Africa, but it is relatively high in developing countries in East Asia, East Europe, and South America. The outlook for patients with advanced stomach cancer is exceedingly dismal, with a survival rate of less than 20% after five years.[4,5]

It is likely that an increase in the use of refrigerators and a decreased reliance on salt for food preservation, an increase in the availability of fresh fruits and vegetables, and the successful treatment of chronic infections with H. pylori have all contributed to a decrease in the incidence of gastric cancer in most parts of the world in recent years.[6] However, it continues to be a serious malignancy harming human health, and it is estimated that in 2008 it may have been responsible for 8% of the total cancer incidence and 10% of the total cancer deaths across the globe.[7,8]

This article analyzes the possible connection between gastric cancer and type 2 diabetes mellitus.

METHODS

Protocol

The regulations that guided the execution of this systematic review were founded on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist. This checklist served as the basis for the regulations.

Eligibility Criteria

This systematic review was developed to analyze papers on "type 2 diabetes mellitus" and “gastric cancer”. These are the topics that were extensively covered in the study that was considered. In order for your work to be considered, the following conditions must be met: 1) Articles must be written in the English language. 2) Articles must have been published after 2017, but prior to the creation of this systematic review. Under no circumstances will the following types of textual contributions be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions without a Digital Object Identifier (DOI), and 3) article reviews and submissions similar to those previously published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from December, 5th 2022 using the PubMed and SagePub databases by inputting the words: "type 2 diabetes mellitus" and “gastric cancer”. Where *("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND ("stomach neoplasms"[MeSH Terms] OR ("stomach"[All Fields] AND "neoplasms"[All Fields]) OR "stomach neoplasms"[All Fields] OR ("gastric"[All Fields] AND "cancer"[All Fields]) OR "gastric cancer"[All Fields])* is used as search keywords.

Data retrieval

The author of the study revised the criteria for what should be included in the study and what should not be included in the study after completing a literature review and reviewing the titles and abstracts of previously published studies. This was done in order to determine what should be included in the study and what should not be included in the study. The new criteria are included in the study's appendix, where they can be discovered.

This was done so that it could be established what parts of the situation should be included in the study and what aspects of the scenario should not be included in the study. This was done so that it could be determined what aspects of the situation should be included in the study. The author reached this conclusion on the necessity of these modifications after conducting research on previously completed and published studies.

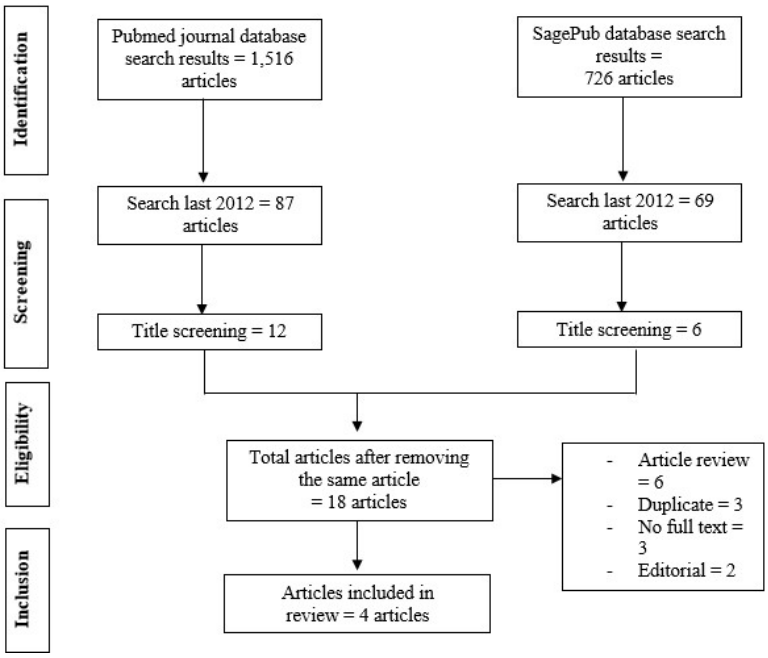

Figure 1. Article search flowchart

During the process of compiling the systematic review, it was determined that the only research projects that were worthy of consideration were those that achieved success in achieving each and every one of the parameters. This meant that the only research projects that were worthy of consideration were those that achieved success in achieving each and every one of the parameters. This was done in order to ensure that the evaluation is as comprehensive as it possibly can be. Specifically, the goal was to: It is possible to collect information about each individual study, such as its title, author, publication date, origin of study location, research study design, and research variables. Some of the information that may be gathered includes the following: The following are some examples of the types of information that might be gathered: Depending on which presentation method you want, this information can be made available to you in a number of different ways.

Quality Assessment and Data Synthesis

In order to select which studies may be taken into consideration, the authors conducted their own independent reviews of a subset of the research that was provided in the titles and abstracts of the papers. After this step, the full texts of the studies that satisfy the inclusion criteria for the systematic review will be studied in order to identify which studies can be utilized as final inclusions for the purposes of the review. This will be done so as to ensure that the review is as accurate as possible. In order to provide an answer to the question "Which studies are available for us to employ for the review?" this will be carried out.

RESULT

A study in Korea showed the fully adjusted hazard ratio (HR) for incident gastric cancer was 1.76 [95% confidence interval (CI) = 1.04–2.97; P = 0.033], when patients were compared based on whether or not they had diabetes at the beginning of the study. When we looked at DM as a time-varying covariate, we found that the fully adjusted HR was 1.66 (95% CI = 1.04–2.68; P = 0.036). There was no significant difference found in the link between diabetes and incidence gastric cancer due to the presence of intestinal metaplasia (P for interaction = 0.61).[9]

Zheng *et al* (2019) conducted a study with 1111,198 participants and showed risk of gastric adenocarcinoma was not increased among participants who had prediabetes (HR = 1.07, 95% confidence interval [CI] = 0.79–1.44), diabetes (HR = 0.77, 95% CI = 0.46–1.29) or any of these exposures (HR = 0.96, 95% CI = 0.73–1.27). In stratified analyses or in analyses that separated cardia and non-cardia gastric adenocarcinoma, there were no relationships found between prediabetes or diabetes and the risk of stomach adenocarcinoma.[10]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Hyo-Joon, 2020[9]	Korea	Retrospective cohort study	195,312	The fully adjusted HR for incident gastric cancer in persons with and without DM at baseline was 1.76 (95% CI = 1.04–2.97; P = 0.033). The fully adjusted HR for time-varying covariate DM was 1.66 (95% CI = 1.04–2.68; P = 0.036). DM and gastric cancer were not affected by intestinal metaplasia (P for interaction = 0.61).
Zheng, 2019[10]	Sweden	Cohort study	111,198	The risk of gastric adenocarcinoma was not increased in participants with prediabetes (HR = 1.07, 95% CI = 0.79-1.44), diabetes (HR = 0.77, 95% CI = 0.46-1.29), or any of these exposures (HR = 0.96, 95% CI = 0.73-1.27) compared to normoglycemic participants. In stratified analyses or analyses separating cardia and non-cardia gastric adenocarcinoma, no associations were found between prediabetes or diabetes and the risk of gastric adenocarcinoma.
Zhou, 2015[11]	China	Clinical trial	978	Hyperglycemia (fasting plasma glucose 6,1 mM) was associated with tumor size, location, and pTNM stage. AQP3 expression in tumor tissue was correlated with plasma glucose levels during fasting. High glucose concentration dose- and time-dependently enhanced AQP3 expression. A significant increase in GC cell migration was inhibited by AQP3 siRNA knockdown in the presence of high glucose concentration. Nonetheless, a high glucose concentration hindered cell growth, and AQP3 knockdown dramatically amplified this impact. The ERK and PI3K/AKT signaling pathways were engaged in the modulation of AQP3 in human GC cells in response to high glucose levels.
Cheung, 2019[12]	Hong Kong	Territory-wide cohort study	46,460	During a median follow-up period of 7.1 years (interquartile range: 4.8–9.3 years), 153 of 46,460 patients (0.33%) were diagnosed with GC at a median age of 72,4 years. A higher incidence of GC was associated with type 2 diabetes (aHR 1.73 [95% CI 1.08–2.50]). Stratified analysis revealed an increase in risk only for cardia cancer (aHR 3.40 [95% CI 1.45–7.97]) and in those with inadequate DM control (time-weighted mean HbA1c 6.0% [42 mmol/mol]; aHR 1.68 [95% CI 1.45–2.67]).

Zhou, et al (2015)[11] showed correlation between hyperglycemia (defined as a fasting plasma glucose level of 6.1 mM or more) and tumor size, location, and pTNM stage. There was a correlation between the expression of AQP3 in tumor tissue and fasting plasma glucose levels. A dose- and time-dependent upregulation of AQP3 expression was seen when a high glucose concentration was present. A high glucose concentration greatly enhanced GC cell movement, and AQP3 knockdown using siRNA was able to eliminate the increase in cell migration that was caused by the high glucose concentration. However, a high glucose concentration was found to impede cell proliferation, and the knockdown of AQP3 considerably increased the extent to which high glucose could exert its inhibitory impact. The effects of high glucose on the expression of AQP3 in human GC cells were found to include both the ERK and PI3K/AKT signaling pathways.
Cheung study showed 153 out of 46,460 patients, or 0.33%, acquired GC at a median age of 72.4 years during a follow-up period that averaged 7.1 years (with an interquartile range of 4.8–9.3 years). The adjusted hazard ratio for developing GC was 1.73, with a 95% confidence interval ranging from 1.08 to 2.79. A higher risk was seen for cardia cancer only in the stratified analysis (adjusted HR 3.40; 95% confidence interval [CI]: 1.45–7.97) and in those with inadequate treatment of their diabetes (time-weighted mean HbA1c 6.0% [42 mmol/mol]; adjusted HR 1.68; 95% confidence interval [CI]: 1.07–2.63).[12]

DISCUSSION

Incidence rates are rising at an alarming rate, making gastric cancer one of the most prevalent forms of malignant gastrointestinal tumors. The only treatment that has shown to be successful for stomach cancer is called radical resection.[13] The incidence rate of postoperative complications of stomach cancer has dramatically decreased as a result of the advancement of surgical procedures. However, factors related to the surgery itself may raise the chance of infections, which may ultimately result in mortality after surgery. In this day and age, with an aging population that continues to expand, the incidence rate of T2DM is raised year by year, and blood glucose level is an essential component that affects the recovery from radical operation for stomach cancer.[14]
Gastric adenocarcinoma was not linked to prediabetes or diabetes in a research. Sub-analysis stratified by variables, removing cases within the first year of follow-up, distinguishing non-cardia and cardia gastric adenocarcinomas, and linear analyses of blood glucose levels showed no connection.[10] The found link was consistent when newly acquired diabetes during follow-up was analyzed as a time-varying covariate, indicating that the higher risk of gastric cancer in DM started early in the disease. Previous large-scale research on diabetes mellitus and gastric cancer used cancer registries or hospital admission data, which are prone to misclassification, inadequate ascertainment, and delayed reporting.[15,16]
Previous studies with large sample sizes that examined the association between diabetes mellitus and gastric cancer identified cancer cases by using cancer registries. In addition, the presence of prevalent subclinical gastric cancer at the beginning of these trials could not be ruled out by these studies. In the current investigation, an experienced endoscopist evaluated each participant using an upper endoscopy at both the beginning of the trial and at several points throughout the

follow-up period. By excluding people who already had stomach cancer at the beginning of the study, we might reduce the risk of both reverse causation and misclassification bias.[17]

In this study, we identified whether or not someone had diabetes based on a laboratory investigation of their fasting glucose levels as well as their medical history. In contrast, a number of the earlier studies that looked at the link between diabetes and stomach cancer relied solely on self-administered questionnaires.[16,17] These studies had a low level of sensitivity and specificity.[18] Study conclusion that there is a greater relationship between DM and gastric cancer than that which was shown in previous Japanese and Korean cohort studies, as well as a systematic review on this topic, could be explained by this aspect.[19]

Diabetes mellitus is a well-known risk factor for a number of different kinds of cancer, most notably liver and pancreatic cancer. Diabetes mellitus (DM) has been linked to an increased risk of developing a number of malignancies, including stomach cancer, and this link may be explained by more than one mechanism.[19] A damaged DNA strand can be the direct result of hyperglycemia, or it can be the indirect result of hyperglycemia if reactive oxygen species are produced. The accumulation of mutations in oncogenes and tumor suppressor genes may be the end result of oxidative stress that is triggered by metabolic processes.[9]

In example, the function of oxidative DNA damage in gastric carcinogenesis may be able to explain how hyperglycemia and H. pylori infection can work together to produce a synergistic effect. A high insulin level, also known as hyperinsulinemia, as well as raised levels of insulin-like growth factors (IGFs), are both associated with type 2 diabetes. Previous research has shown that obesity is linked to an increased risk of developing gastric and heart cancer. Insulin resistance and the subsequent hyperinsulinemia have been proposed as potential explanations for this condition. Insulin resistance may potentially have a role in the development of diabetes-related gastric cancer, despite the fact that obesity was not found to be directly linked to non-cardiac gastric cancer.[19]

It is possible that the overexpression of IGFs and the heterogeneous expression of IGF-binding proteins, also known as IGFBPs, all play a significant part in the progression of gastric cancer. Hyperinsulinemia may also cause a downregulation of IGFBP levels, which contributes in a roundabout way to increased IGF levels. It has also been proven that intestinal metaplasia is a risk factor for gastric cancer. Those in the current study who had both diabetes and intestinal metaplasia had an almost fivefold increased chance of acquiring gastric cancer compared to participants in the study who did not have either DM or metaplasia.[19]

It has been hypothesized that patients who have intestinal metaplasia may derive more benefit from undergoing endoscopic screening for gastric cancer on an annual basis, as opposed to the biennial screening that is recommended for persons with a moderate risk of developing the disease. Based on our findings, we believe that people who have both diabetes and metaplasia should undergo an endoscopic examination that is particularly thorough. It is necessary to conduct additional study in order to personalize the screening interval for stomach cancer in this high-risk population.[19]The present study has many strengths, including a large sample size, the availability of endoscopic data at baseline and during follow-up, the pathologic confirmation of cases of gastric cancer, the availability of fasting glucose levels and other information regarding DM at baseline and during follow-up, and the availability of high-quality data on multiple demographic, lifestyle, medical history, and examination variables. In addition, the men and women who make up the population of our research study are of a middle-aged age. This means that they are less likely than older cohorts to be affected by selection bias, as well as biases caused by mortality, comorbidities, and medication use.[19]

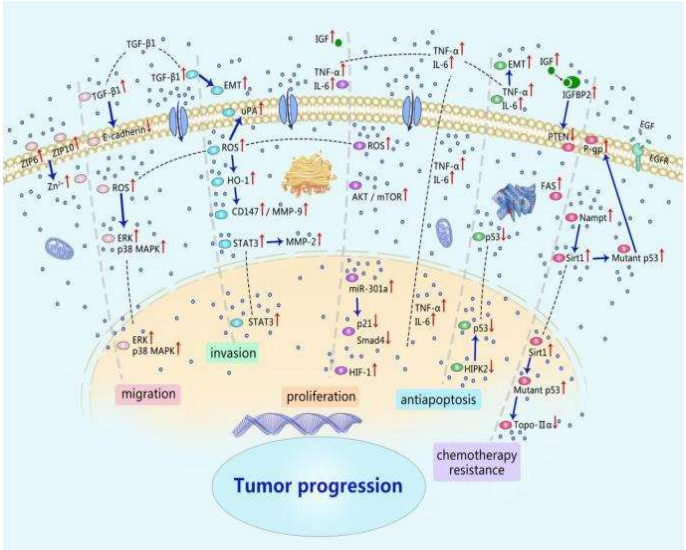

Figure 2. Mechanisms underpinning the promotion of cancer development by hyperglycemia

A higher chance of developing gastric adenocarcinoma may be associated with certain aspects of one's lifestyle, such as smoking, drinking, level of physical activity, and food. In the current investigation, the multivariable analyses accounted for six of the most relevant confounders, and even after accounting for all twelve factors, the findings did not significantly

shift in response to these additional adjustments (data not shown). In point of fact, diabetes patients may adopt new patterns of behavior in response to receiving their diagnosis.[20]

Following their diabetes diagnosis, these participants had a greater propensity to adopt a healthier diet, such as increasing their consumption of fresh fruit and vegetables while simultaneously decreasing their consumption of salt and total energy, and they were also more likely to give up smoking. These modifications in lifestyle might protect these patients from getting gastric adenocarcinoma, and as a result, they might either negate or disguise a potential relationship between diabetes and gastric adenocarcinoma.[21,22]

A high blood sugar level, or hyperglycemia, can encourage the growth, proliferation, invasion, and migration of cancer cells, particularly those that affect the breast, liver, bladder, pancreas, colorectum, and endometrial. An in vitro and in vivo study found that it can also boost human gastric cancer cell proliferation and development while also inducing chemoresistance to the chemotherapy drug 5-fluorouracil in GCa cells.[23] Zhou et al. found that hyperglycemia with a preoperative fasting plasma glucose level of more than 6.1 mM was linked with the size of the tumor, its location, and the late stage of the cancer in 978 individuals who had GCa. In individuals who had greater levels of fasting plasma glucose, the expression of aquaporin 3 (AQP3, a biomarker of GCa) was also shown to be elevated in the resected tumors.[11]

The expression of AQP3 was elevated by high glucose concentrations in a dose- and time-dependent manner, as shown by additional in vitro tests conducted in human GCa cells of MGC803 and SGC7901. These investigations were conducted in human GCa cells of MGC803 and SGC7901. When compared to a glucose concentration of 100 mg/dL, the other in vitro and in vivo study that was conducted by Zhao et al. suggested that hyperglycemia at 450 and 900 mg/dL would stimulate cancer cell proliferation and inhibit cancer cell response to the chemotherapeutic drug of 5-fluorouracil. This was in contrast to the finding that a glucose concentration of 100 mg/dL would result in no change in cancer cell proliferation or response to the drug.[23]

CONCLUSION

Research shows a consistent link between diabetes and an increased risk of gastric cancer. This shows that interventions to reduce the patient's blood sugar levels must be carried out optimally.

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