THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 4, p.56-60

TYPE II DIABETES MELLITUS AS AN IMPORTANT RISK FACTOR OF CANCER OF PANCREAS: FINDINGS OF NARRATIVE REVIEW

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Received 27.08.2020; accepted for printing 07.08.2021

ABSTRACT

Diabetes mellitus is one of the foremost concerns in high as well as low-middle income nations. Around 45% of cases of pancreatic carcinoma are expected to appear as incident cases of diabetes mellitus; nevertheless, the type of relationship between type two diabetes mellitus and pancreatic carcinoma is however controversial. Therefore, we carried out a narrative review to synthesize the findings of the relationship between diabetes mellitus and cancer of the pancreas.

We approached Google Scholar and PubMed to carry out the searches for relevant articles. We undertook a narrative review of eligible research articles that were available in the English language in developed and developing countries from 2015 to 2020. All primary research articles were examined for information pertinent to the objective. All references of the eligible articles were also reviewed to make sure to include all relevant articles in the review.

The included studies explored the association between diabetes mellitus and malignancy of the pancreas. We found the results of the review to be supportive of our hypothesis. Numerous biologic pathways and processes have been highlighted as a shred of evidence that alludes to the association between diabetes mellitus and malignancy of the pancreas. Abnormalities in metabolism, immunologic pathways, and hormonal features of diabetes mellitus may increase the risk of cancer development.

Further, studies have shown that increased production of insulin and insulin-like growth factors may increase the probability of malignancy of the pancreas by upregulating cellular proliferation and thereby abnormal cancerous cells.

There is evidence that shows that diabetes mellitus increases the risk of several cancers such as malignancy of the pancreas. On the basis of the evidence from this review, it is recommended for clinicians to screen people for diabetes mellitus and also monitor the existing patients with diabetes mellitus to screen for pancreatic cancer in a timely manner.

KEYWORDS: *diabetes mellitus, pancreatic cancer*

INTRODUCTION

Cancer of the pancreas is found to be the most prevalent malignancy across the globe and a five-year survival rate is about 7%, and it has been found that for the majority of patients, mortality ensues in six months following diagnosis [*Ryan D, Hong T, 2014; Mizrahi J et al., 2020*]. Cancer of the pancreas holds a miserable prognosis due to a five-year survival rate of < 5%, and most of the patients die within six months after they are diagnosed with malignancy [*Hezel A et al., 2006*]. The incidence and rate of mortality of this cancer are about 7.5% and 7.0%, respectively after adjusting for age. Furthermore, the majority of the patients are not considered eligible for the surgery due to the locally advanced spread of cancer in the body [*Kuuselo R et al., 2007*].

It is imperative to identify high-risk individuals to increase survival and reduce the morbidity and mortality associated with the cancer of the pancreas. In order to do this, causes and risk factors of pancreatic cancer would need to be identified as its etiology remains uncertain except few demographic and behavioral reasons such as age, smoking status, enhanced body weight, and positive

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family history of pancreatic cancer [*Wiseman M, 2008*]. For example, around one-quarter to one-third of pancreatic cancer is explained by smoking while less than 10% of the diagnosed cases are reported among <50 years old individuals [*Lowenfels A, Maisonneuve P, 2005*]. In addition to this, compelling data have suggested that Diabetes mellitus (DM) increases the risk of numerous malignancies, such as malignancy of the pancreas [*Giovannucci E et al., 2010*], and DM can increase the stage of cancer and death from cancer [*Griffiths R et al., 2012; Toriola A et al., 2014*]; however, the results are found to be conflicting. Additional, it is not still established whether DM is a disposing risk factor or a possible result of tumor growth, or both [*Gapstur S et al., 2000*].

Around 45% of cases of pancreatic carcinoma are expected to appear as incident cases of DM; nevertheless, the type of relationship between type two DM and pancreatic carcinoma is, however, contentious [*Ben Q et al., 1990*]. For example, there is a debate about whether DM leads to malignancy of the pancreas or is the result of malignancy of pancreas and the existing evidence from individual observational studies considers DM as a potential cause for malignancy of pancreas [*Esposito K et al., 2012*]. However, the evidence from such studies needs to be synthesized after reviewing the findings critically. Therefore, we carried out a narrative review to synthesize the findings of the association between DM and malignancy of pancreas. The worse prognosis of pancreatic cancer and the absence of effective treatment for a long time make it worth studying the pathogenesis of cancer and its association with the DM.

Materials and methods

We approached Google Scholar and PubMed to carry out the searches for relevant articles. We undertook a narrative review of eligible research articles that were available in the English language in developed and developing countries from 2015 to 2020. All primary research articles were examined for information pertinent to the objective. All research studies in the above-mentioned databases were searched using search terms such as “association between DM and Pancreatic cancer”, “relationship between DM and malignancy of pancreas”, “DM as a risk factor for malignancy of pancreas”, “DM and malignancy of pancreas”, “Type 2 DM leads to malignancy of pancreas”, “Type 2 DM and malignancy of pancreas”.

We included studies from high and low-middle-income countries and assessed the full-text articles of the eligible studies.

All references of the eligible articles were also reviewed to make sure to include all relevant articles in the review. After searching for different databases and following the above criteria, finally, studies having full-text articles were assessed and were made part of the review.

Results of the Narrative review

Mechanism of action for the relationship between DM and malignancy of pancreas

Type 2 DM is a metabolic disorder with a characteristic increased level of blood glucose levels that happens as a result of malfunctioning insulin excretion by islets of pancreas while responding to increased blood glucose levels after the meal as well as insulin resistance to insulin at the periphery and production of glucose in a dysregulated manner [*Unger R, Orci L, 2010*]. There is a relationship between DM and obesity that has risen over time worldwide. Among obese individuals, the insulin response further deteriorates at the cellular level, which means there is increased resistance of tissues to insulin, increases the burden on the pancreas to produce increased amounts of insulin [*Unger R, Orci L, 2010*]. This in turn will result in an increased amount of insulin in the blood, which is further triggered by genes and environmental factors [*Stumvoll M et al., 2005*].

Insulin works to regulate the levels of glucose in the blood and also regulate the metabolism of lipids and by acting as a possible growth factor in the multiplication of cells and increases in the formation of blood vessels. Though DM is likely to rising the probability of various forms of cancers, the threat to cause malignancy of the pancreas has been found to be very high

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

[*Burney S et al., 2014*]. Cancerous alteration of pancreatic tissues with more changes in the epithelial cells of ducts of exocrine part of the pancreas, when allied with raised production of insulin impending from the endocrine part of the pancreas, nurture quickly and perhaps such a relationship might be the reason for the distressing consequence of cancer of the pancreas [*Fokas E et al., 2015*].

Results of studies supporting our hypothesis

The included studies explored the association between DM and malignancy of the pancreas. The findings of the review were supportive of our hypothesis [*Li D et al., 2015*]. For example, a study conducted by Donghui Li and co-authors found that newly diagnosed DM is a substantial impartial determinant for the hazard of death in patients with malignancy of the pancreas (p=0.002). Authors found that DM overall and newly diagnosed DM, in particular, is related to adverse consequences for pancreatic cancer [*Li D et al., 2015*]. Likewise, another observational study was performed by Yun Xia and colleagues who identified cases of malignancy of the pancreas from some database in the UK and identified the controls randomly independent of DM [*Lu Y et al., 2015*]. This was followed by matching factors such as calendar time, age, and sex. Authors found a higher likelihood of pancreatic cancer in patients with Type 2 DM with an Odds ratio of more than 2 [*Lu Y et al., 2015*]. These results indicated that Odds of malignancy of pancreas among patients with DM were two times the Odds of malignancy of pancreas among patients without DM. Authors further reports that patients who were on insulin were 25.57 times likely to develop the pancreatic cancer with imprecise 95% confidence intervals. However, patients on medications such as sulphonylureas were 2.22 times likely to develop the cancer and those who reported using metformin were 1.46 times likely to develop pancreatic cancer when compared to those who were on no medications. According to authors, newly diagnosed DM appears to be an unbiased risk factor for cancer of pancreas. The association between medications for DM and malignancy of pancreas seem to differ in magnitude and precision with higher probability of malignancy of pancreas among insulin users [*Lu Y et al., 2015*].

Another observational study was conducted by using the National Diabetes Register of Sweden to assess the association between DM and the probability of pancreatic cancer [*Sadr-Azodi O et al., 2015*]. They identified 10 controls randomly for each case of the pancreas and matched them with cases on age, sex, and other characteristics related to DM with a ratio of 1:10 cases to controls between 2005 to 2011 [*Sadr-Azodi O et al., 2015*]. According to the authors, diabetic patients with increased concentrations of HBA1c were at higher risk of acquiring malignancy of pancreas with an Odds ratio of about 2 and significant results (p-value: <0.05). The authors also highlighted that there is a lead time of numerous to detect pancreatic cancer among diabetic patients in a timely manner [*Sadr-Azodi O et al., 2015)*].

Another study was conducted in China using data from four cancer registries in four different hospitals [*Zheng Z et al.,2016*]. The authors selected controls by including family members of non-pancreatic cancer patients and conducted interviews with them to explore the correlation between DM and the probability of malignancy of the pancreas. Authors found that apart from smoking, obesity, family history, DM appeared to be the strongest risk factor for malignancy of the pancreas and recommended designing appropriate interventions to prevent pancreatic cancer [*Zheng Z et al.,2016*]. Another study was conducted to find the independent effect of DM on the malignancy of the pancreas on 817 cases and 1756 controls [*Antwi S et al., 2016*]. The study findings revealed three times more danger of malignancy of the pancreas among patients with DM than non-diabetic patients in addition to other risk factors including pro-inflammatory diet and smoking. This was followed by another prospective study on about 512,000 individuals from various areas of China [*Pang Y et al., 2017*]. This large epidemiological study found about 2-fold increase in the risk of pancreatic cancer among diabetic patients with statistically significant results. The risk of cancer was also substantially greater in diabetic patients who were diagnosed with longer duration of DM and patients with previous diagnosis of DM had about 52% excess risk of malignancy of pancreas [*Pang Y et al., 2017*]. Similarly, Setiawan V.W. and co-authors (2019) conducted a research study in 2018 on about 50,000 African American and Latinos in the large cohort. The study found gretaer

than 2-fold increase probability of malignancy of pancreas among diabetic patients, thereby further endorsing the findings of previously conducted observational studies [*Setiawan V et al., 2019*].

Conclusion

Diabetes mellitus is considered an important concern in both high and low-middle income areas. There is a piece of evidence that shows that DM increases the risk of several cancers including pancreatic cancer. Numerous biologic pathways and processes have been highlighted as a shred of evidence that alludes to the correlation between DM and malignancy of the pancreas. Abnormalities in metabolism, immunologic pathways, and hormonal features of DM may increase the risk of cancer development. Further, studies have shown that increased production of insulin and insulin-like growth factors may increase the probability of malignancy of the pancreas by upregulating cellular proliferation and thereby abnormal cancerous cells. Based on the evidence from this review, it is recommended for clinicians to screen people for DM and also monitor the existing patients with DM to screen for pancreatic cancer in a timely manner.

REFERENCES

1. *Antwi SO, Oberg AL, Shivappa N, Bamlet WR, Chaffee KG., et al (2016).* Pancreatic cancer: associations of inflammatory potential of diet, cigarette smoking and long-standing diabetes. Carcinogenesis. 37(5): 481-490
2. *Ben Q, Cai Q, Li Z, Yuan Y, Ning X., et al (2011).* The relationship between new-onset diabetes mellitus and pancreatic cancer risk: a case-control study. European journal of cancer (Oxford, England: 1990). 47(2): 248-254
3. *Burney S, Irfan K, Saif MW, Masud F (2014).* Diabetes and pancreatic cancer. JOP: Journal of the pancreas. 15(4): 319-321
4. *Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D (2012).* Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes care. 35(11): 2402-2411
5. *Fokas E, O'Neill E, Gordon-Weeks A, Mukherjee S, McKenna WG, Muschel RJ (2015).* Pancreatic ductal adenocarcinoma: From genetics to biology to radiobiology to oncoimmunology and all the way back to the clinic. Biochimica et biophysica acta. 1855(1): 61-82
6. *Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A (2000).* Abnormal glucose metabolism and pancreatic cancer mortality. Jama. 283(19): 2552-2558
7. *Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM., et al (2010).* Diabetes and cancer: a consensus report. Diabetes care. 33(7): 1674-1685
8. *Griffiths RI, Danese MD, Gleeson ML, Valderas JM (2012).* Epidemiology and outcomes of previously undiagnosed diabetes in older women with breast cancer: an observational cohort study based on SEER-Medicare. BMC cancer. 12: 613
9. *Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, DePinho RA (2006).* Genetics and biology of pancreatic ductal adenocarcinoma. Genes development. 20(10): 1218-1249
10. *Kuuselo R, Savinainen K, Azorsa DO, Basu GD, Karhu R., et al (2007).* Intersex-like (IXL) is a cell survival regulator in pancreatic cancer with 19q13 amplification. Cancer research. 67(5): 1943-1949
11. *Li D, Mao Y, Chang P, Liu C, Hassan MM., et al (2015).* Impacts of new-onset and long-term diabetes on clinical outcome of pancreatic cancer. American journal of cancer research. 5(10): 3260-3269
12. *Lowenfels AB, Maisonneuve P (2005).* Risk factors for pancreatic cancer. Journal of cellular biochemistry. 95(4): 649-656
13. *Lu Y, García Rodríguez LA, Malgerud L, González-Pérez A, Martín-Pérez M., et al (2015).* New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. British journal of cancer. 113(11): 1607-1614
14. *Mizrahi JD, Surana R, Valle JW, Shroff RT (2020).* Pancreatic cancer. Lancet (London, England). 395(10242): 2008-2020

15. *Pang Y, Kartsonaki C, Guo Y, Bragg F, Yang L., et al (2017).* Diabetes, plasma glucose and incidence of pancreatic cancer: A prospective study of 0.5 million Chinese adults and a meta-analysis of 22 cohort studies. International journal of cancer. 140(8): 1781-1788

16. *Ryan DP, Hong TS, Bardeesy N (2014).* Pancreatic adenocarcinoma. New England Journal of Medicine. 371(11): 1039-1049

17. *Sadr-Azodi O, Gudbjörnsdottir S, Ljung R (2015).* Pattern of increasing HbA1c levels in patients with diabetes mellitus before clinical detection of pancreatic cancer - a population-based nationwide case-control study. Acta oncologica (Stockholm, Sweden). 54(7): 986-992

18. *Setiawan VW, Stram DO, Porcel J, Chari ST, Maskarinec G., et al (2019).* Pancreatic Cancer Following Incident Diabetes in African Americans and Latinos: The Multiethnic Cohort. Journal of the National Cancer Institute. 111(1): 27-33

19. *Stumvoll M, Goldstein BJ, van Haeften TW (2005).* Type 2 diabetes: principles of pathogenesis and therapy. Lancet (London, England). 365(9467): 1333-1346

20. *Toriola AT, Stolzenberg-Solomon R, Dalidowitz L, Linehan D, Colditz G (2014).* Diabetes and pancreatic cancer survival: a prospective cohort-based study. British journal of cancer. 111(1): 181-185

21. *Unger RH, Orci L (2010).* Paracrinology of islets and the paracrinopathy of diabetes. Proceedings of the National Academy of Sciences of the United States of America. 107(37): 16009-16012

22. *Wiseman M (2008).* The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. The Proceedings of the Nutrition Society. 67(3): 253-256

23. *Zheng Z, Zheng R, He Y, Sun X, Wang N., et al (2016).* Risk Factors for Pancreatic Cancer in China: A Multicenter Case-Control Study. Journal of epidemiology. 26(2): 64-70

THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 4

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The Journal is founded by
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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "collage" LTD
Director: A. Muradyan
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OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY