Type 2 Diabetes Mellitus and Its Association with the Risk of Pancreatic Carcinogenesis: A Review

Belete Biadgo and Molla Abebe
Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

The prevalence of diabetes mellitus (DM) and associated diseases such as cancers are substantially increasing worldwide. About 80% of the patients with pancreatic cancer have glucose metabolism alterations. This suggests an association between type 2 DM and pancreatic cancer risk and progression. There are hypotheses that show metabolic links between the diseases, due to insulin resistance, hyperglycemia, hyperinsulinemia, low grade chronic inflammation, and alteration in the insulin-insulin-like growth factor axis. The use of diabetes medications can influence the extent of carcinogenesis of the pancreas. This study briefly reviews recent literature on investigation of metabolic link of type 2 DM, risk of carcinogenesis of the pancreas and their association, as well as the current understanding of metabolic pathways implicated in metabolism and cellular growth. The main finding of this review, although there are discrepancies, is that according to most research long-term DM does not raise the risk of pancreatic cancer. The longest duration of DM may reflect hypoinsulinemia due to treatment for hyperglycemia, but recent onset diabetes was associated with increased risk for pancreatic cancer due to hyperinsulinemia and hyperglycemia. In conclusion, the review demonstrates that type 2 DM and the duration of diabetes pose a risk for pancreatic carcinogenesis, and that there is biological link between the diseases. (Korean J Gastroenterol 2016;67:168-177)

Key Words: Type 2 diabetes mellitus; Pancreatic neoplasms

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, action, or both. Several pathogenic processes are involved in the development of DM. These range from autoimmune destruction of the cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Deficient insulin action results from inadequate insulin secretion and diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Type 2 diabetes mellitus (T2DM) consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. It comprises over 90% of all DM cases and is usually diagnosed after 40 years of age, although recently much younger cases are being reported. Poorly controlled T2DM is associated with an array of microvascular and macrovascular complications. Longitudinal and cross-sectional studies have demonstrated that the earliest detectable abnormality in T2DM is an impairment of the body’s ability to respond to insulin. Genetic susceptibility and environmental factors are the most likely triggers of T2DM. The main function of the pancreas is to produce endocrine hormones and digestive enzymes that help break down carbohydrates, fats and proteins. The link between diabetes and cancer exists because T2DM is associated with increased insulin production; insulin causes the growth of cells and the
proliferation of blood vessels in the pancreas that generates a hospitable environment for tumor formation.\(^6\)

Pancreatic cancer (PC) is a malignant tumor of the pancreas, and one of the most tragic and least understood of cancers, affecting the cells that produce insulin and glucagon.\(^6\) The majority of PC originates from the ductal epithelial cells of the exocrine portion of the pancreas. There is extensive interaction between the endocrine and exocrine portions of the pancreas during pancreatic carcinogenesis.\(^6\) It is characterized by an increased incidence in Western industrialized countries, an extremely poor median survival of four to six months after diagnosis and with an overall five-year survival of less than 4%.\(^7\)

The incidence and number of deaths caused by PC have been gradually rising, although incidence and mortality of other common cancers have been declining.\(^6\) Inability to detect PC at an early stage, its aggressiveness, and the lack of effective systemic therapy are responsible for the rapid death of PC patients.\(^9\) The poor outcome is a strong motivation for epidemiological research designed at identifying and reducing risk factors for PC. Besides age and genetic risk factors, several lifestyle and environmental factors, such as smoking, obesity, low physical activity and alcohol consumption are associated with PC.\(^10\)

T2DM is associated with PC, but it is unclear whether DM is a causal factor or the result of subclinical malignancy.\(^11\) T2DM may directly promote the progression of PC by pancreatic duct enlargement and hypertension, as well as increased tumor size. Up to 80% of PC patients are either hyperglycemic or diabetic, both of which can be detected in the pre-symptomatic phase. Hyperglycemia and glucose tolerance aberrations may be the first easily testable clinical manifestation of DM.\(^12\)

At question is whether coincidence of diabetes and the risk of certain cancers is largely due to shared risk factors, or whether diabetes itself, and the specific metabolic disorders typical of diabetes, increase the risk of some types of cancer.\(^13\) The development of DM within a few years of a PC diagnosis suggests an effect of the tumor, whereas DM of longer duration is more likely to contribute to the development of cancer.\(^14\) T2DM and PC are linked, but researchers have found it difficult to determine which influences the other.\(^15\) Based on the findings from several retrospective and prospective observational studies, T2DM and glucose intolerance are fairly reliable, albeit somewhat debatable, risk factors for PC.\(^16\)-\(^19\)

A helpful perspective can be obtained by examining research focusing on T2DM in the setting of PC to gain further understanding of the link between T2DM and PC. In developing countries, especially in Ethiopia, T2DM patients are not screened for PC, although glycemic control is used for management of DM to control micro and macro vascular complication. Therefore, this review examines the metabolic link and association between T2DM and the risk of pancreatic carcinogenesis, and provides the most reliable information on the magnitude of association.

**MAIN SUBJECTS**

1. **Mechanism of T2DM–associated pancreatic carcinogenesis**

Carcinogenesis is a multifaceted process whereby normal cells go through multiple genetic hits before the full neoplastic phenotype of growth, invasion, and metastasis occurs. This process of malignant transformation can be divided into multiple steps: initiation, promotion and progression.\(^20\) Factors that affect one or more steps of this pathway could be associated with cancer incidence or mortality. The mechanism of the association between DM and PC is mysterious but most hypothesized mechanisms underlying the association between T2DM and PC include hyperinsulinemia, insulin resistance (IR), elevated levels of circulating insulin-like growth factors (IGFs), hyperglycemia and chronic inflammation that influences tumor growth.\(^20\)

The pancreas is exposed to high concentrations of endogenously produced insulin. The causal nature of the association with PC risk is complicated by the fact that abnormal glucose metabolism may be a consequence of PC. However, a positive association between T2DM and PC risk has been found when restricted to T2DM that precedes the diagnosis of PC by at least five years.\(^21\)

1) **Hyperinsulinemia and insulin resistance**

Recent epidemiological and clinical evidence points to a link between IR and PC. Increased risk of cancer among IR patients is explained in part by overproduction of reactive oxygen species (ROS) that can damage DNA, contributing to mutagenesis and carcinogenesis. On the other hand, it is possible that the abundance of inflammatory cells in adipose tissue of obese and T2DM promotes systemic inflammation. Such adiposity is common with hyperinsulinemia and IR,
leading to a tumorigenic environment. Both insulin and IGF-1 have affinity for both the insulin receptor and IGF-1 receptor (IGF-1R) because of similar structural homology. However, it is important to recognize that insulin’s affinity for the insulin receptor is 1,000 fold greater than for IGF-1R. Both IGF-1 and IGF-1R tend to have stronger mitogenic and anti-apoptotic effects, and the hyperinsulinemia that occurs in IR individuals may enhance this effect.

IR status, characterized by hyperinsulinemia, is associated with an increased risk for a number of malignancies, including carcinomas of the breast, prostate, colon, pancreas, and kidney. The insulin cancer hypothesis proposes that chronic hyperinsulinemia reduces concentrations of IGF binding protein (IGFBP-1 and -2), leading to increased tissue levels of IGF-1, crucial in the development and progression of cancers. Hyperinsulinemia may also accelerate tumor growth indirectly through its effects on IGF-1. Cancer cells over-express insulin and IGF-1 receptors, and insulin reduces the hepatic production of IGFBP-1 and -2. This leads to increased levels of free circulating physiologically active IGF-1. This could act as a growth stimulus in cancer cells that express such receptors. Hyperinsulinemia stemming from IR may happen for many years before diabetes diagnosis, with widespread effects. Normally, when insulin binds to its receptors, it activates two pathways: the metabolic pathway and the mitogenic pathway.

Insulin resistance hinders the metabolic pathway, which is the pathway that increases transport of glucose into cells, stimulates glycogen synthesis, and suppresses liver gluconeogenesis. In the absence of insulin’s normal postprandial inhibition activity lipolysis, circulating free fatty acid levels important to the pathogenesis of IR and liver triglyceride production rise, which contributes to atherogenic dyslipidemia. In contrast, IR does not inhibit activation of the mitogenic pathway that promotes proliferation of normal and cancerous cells. Chronic hyperinsulinemia results, leading to a chain of metabolic responses, including changes in IGFBP that result in increased tissue availability of both IGF-1 and -2. Insulin itself is a growth promoting hormone with mitogenic (but not mutagenic) effects and diabetes associated cancer cells express insulin and IGF-1 receptors which play a key role in cell growth and differentiation.

Experimental evidence on animal studies complemented by case studies in humans demonstrate the critical role of IGF in all stages of mammalian growth. IGFBP-1 is suppressed by insulin; this raises the levels of bioavailable IGF-1. Furthermore, insulin up-regulates the bioavailability of IGFs by reducing hepatic production of IGFBP.

The mitogenic and anti-apoptotic activities of IGF-1 are more potent than those of insulin and may act as growth stimuli in cells expressing insulin and the IGF-1R. IGF-1 and IGF-1R are highly expressed in PC cells. IGF-1-mediated signaling transduction increases proliferation, invasion, and expression of angiogenesis mediators and decreases apoptosis in PC cells. IGF-1R mediated initiation of signal transduction activates important intracellular signal pathways, including the Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase/Akt/Pi3K) mammalian target of rapamycin (mTOR) pathways.

Furthermore, in IR states, T2DM causes impairment of downstream glucose transporter 4 (GLUT4) translocation by disruption of insulin receptor substrate-1 (IRS-1)-associated PI3K signaling in the metabolic pathway of insulin. Insulin, to a lesser degree than IGF-1, motivates cellular growth and protein synthesis through the protein kinase B (PKB) system and activation of mTOR. Abnormal IRS-1 phosphorylation from over activation of mTOR creates a negative feedback loop that attenuates the metabolic pathway in hyperinsulinemia. IRS-2 expression by insulin phosphorylation leads to increased extracellular signal regulated kinase (ERK) activation; MAPK because the mitogen pathways mediated by mTOR and Ras remain intact. This drive towards the mitogenic pathway with hyperinsulinemia leads to enhanced cell growth and survival. Therefore, the leading hypothesis for the relationship between T2DM and PC is that IR and consequently hyperinsulinemia may promote tumor cell growth directly via insulin receptors or indirectly via the IGF-1R.

The shared metabolic factors underlying both T2DM and cancer, including visceral adiposity, inflammation, hyperglycemia, and hyperinsulinemia, lead to increased IRS, stimulating the phosphorylation of Ras signaling proteins, and potentially increasing tumor cell growth and proliferation. IRS-associated PI3K signaling is compromised by IR states, such as in T2DM, and downstream GLUT4 translocation is disrupted. This disruption drives PI3K signaling towards AKT/mTOR. AKT and mTOR can affect both the metabolic and mitogenic pathway, but because of the signaling dysfunction, AKT and mTOR are driven towards the mitogenic pathway.
Insulin and IGF receptors form a complex network of cell surface receptors; homodimers and heterodimers have been described, and all function to mediate insulin and IGF responses. The majority of cancer cells express insulin and IGF-1Rs; the A isoform of the insulin receptor is frequently expressed. The ‘A’ receptor isoform can encourage insulin-mediated mitogenesis, even in cells deficient in IGF-1Rs. In addition to its metabolic functions, the insulin receptor is accomplished in stimulating cancer cell proliferation and metastasis. Because most glucose uptake in cancer cells is constitutively high and independent of insulin binding to its receptor, the effects of insulin receptor activation on neoplastic cells may relate more to cell survival and mitogenesis than to enhanced glucose uptake.

Multiple signaling pathways are activated after IGF-1Rs interact with their ligands by phosphorylating adaptor proteins, most notably the IRS family. The initial kinase event is linked to downstream signaling pathways. Once activated these signaling pathways may stimulate multiple cancer phenotypes including proliferation, protection from apoptotic stimuli, invasion, and metastasis, potentially enhancing the progression of many types of cancer cells. It is also clear that during hyperglycemia, IGF may stimulate normal cells that are involved in cancer progression that allows IGF-1 to stimulate vascular smooth muscle cell proliferation and migration. Although this process has been linked to the pathophysiology of atherosclerosis, abnormal vascular growth is also a hallmark of cancer.

2) Hyperglycemia

Laboratory studies suggest that higher circulating glucose may support malignant cell growth. Biologically based mass spectrometry techniques document that proliferating tumor cells preferentially use glucose to synthesize the ribose 5-phosphate required for nucleic acid synthesis.

Prospective cohort and case-control studies show that hyperglycemia is associated with increased free radical formation and may lead to the development of advanced glycation end products (AGEs) that can increase inflammation. These studies also report the link between elevated hemoglobin A1C and other measures of hyperglycemia with an increased risk of colorectal, pancreatic, endometrial, and other cancers. ROS, produced due to activation of various metabolic pathways like polyol pathway, auto oxidation of glucose, lipid peroxidation and Maillard’s reaction, appear to be linked to PC, suggested to be mitogenic and capable of stimulating cell proliferation. Moreover, hyperglycemia IR, hyperinsulinemia and inflammation can cause DNA damage, boost the invasive and migratory activity of PC cells via hydrogen peroxide and the increased expression of urokinase plasminogen activator (uPA). Hyperglycemia can attenuate antioxidant enzyme activity and in turn create a state of oxidative stress.

3) Chronic inflammation

Inflammatory cytokines, ROS, and mediators of inflammatory pathways, such as cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NFκB) are associated with oncogene expression, silencing of tumor suppressor genes, and affect the cell cycle, all of which may facilitate pancreatic carcinogenesis. Chronic, low-grade inflammation can result from DNA damage and create an environment in which more damage occurs.

Adipose tissue is an active endocrine organ recognized as a low-grade inflammatory state in which overproduction of certain molecules, such as free fatty acids, interleukin-6, monocyte chemo attractant protein, plasminogen activator inhibitor 1 (PAI-1), adiponectin, leptin, and tumor necrosis factor alpha (TNF-α) that might play an etiologic role in regulating malignant transformation or cancer progression. Adiponectin increases fatty acids oxidation, which lowers circulating free fatty acids and prevents IR, and it exerts an anti-atherosclerotic effect, while augmenting endothelial nitrous oxide production and protecting the vasculature by reducing platelet aggregation and vasodilation. Apart from causing metabolic dysfunction, adiponectin deficiency may also contribute to cardiovascular disease, IR, and a wide array of cancers.

The decrement of adiponectin precedes the development of IR and myocardial infarction in humans; low levels of adiponectin are likely to be a causal component of those disorders. A study in Pima Indians shows individuals with high levels of adiponectin were less likely to develop T2DM,
suggesting that high adiponectin concentration has anti-inflammatory, anti-apoptotic and pro-angiogenic activities, protective factor against development of T2DM.54,55

2. Epidemiological evidences for type 2 diabetes mellitus and pancreatic cancer

The prevalence of DM has increased dramatically around the globe and is rapidly becoming an overwhelming public health problem in developing countries.56 An estimated 366 million people were living with DM in 2011. The number is expected to grow to 552 million by 2030, and the largest age group currently affected by DM is between 40-59 years. The African continent is expected to experience the highest increase in the coming years with estimated increase in prevalence rates of 98% for sub-Saharan Africa, and 94% for North Africa and the Middle East and 20% increase in developed countries.57,58

A 2010 consensus report from a panel of experts chosen jointly by the American Diabetes Association and American Cancer Society suggested that people with T2DM are at an increased risk for many types of cancer.16,50,59-61 Evidence from observational studies suggests that some medications used to treat hyperglycemia are associated with changed risk of PC.50 For more than 50 years, clinicians have reported the occurrence of patients with concurrent DM and PC.62 However, research as early as 1959 stated that although studies examining the association between DM and cancer were conducted over several years, there was no conclusive evidence of a positive association. Subsequently, an association between the diseases was identified in the 1960s in population based studies.63

PC is the fourth or fifth most common cause of cancer deaths in economically developed countries.64-66 In the European Union, 29,600 deaths in men and 29,900 deaths in women due to PC were estimated for 2004.65 The bilateral causality between the diseases has been widely documented.13,67

Epidemiological studies clearly indicate that the risk of PC is increased in DM patients, but most studies focus on T2DM. The recent increase in the prevalence of T2DM is thought to have contributed to a parallel rise in the incidence of PC.68 Worldwide, the prevalence of cancer is difficult to establish because many areas do not have cancer registries, but in 2008 there were an estimated 12.4 million new cancer cases diagnosed.69 The most commonly diagnosed cancers were those of the lung, breast, and colorectal, whereas the most common causes of cancer deaths were lung, stomach, pancreas and liver cancer.68 It has long been known that PC is associated with DM, and recent studies have revealed that about 85% of patients diagnosed with PC have impaired glucose tolerance.70

3. The association between type 2 diabetes mellitus and the risk of developing pancreatic cancer

Assessing the relationship between DM and the risk of PC poses challenges. Some epidemiological studies observe a relationship between the presence of T2DM and the development of PC. There are a number of potentially plausible explanations for the observed association between T2DM and PC, including shared risk factors, and metabolic derangements such as the metabolic syndrome. IR and hyperinsulinemia are hallmarks of cancers associated with these conditions.51,71 Although there are proposed mechanisms of diabetes related pancreatic carcinogenesis, epidemiological studies clearly indicate that DM is positively associated with an increased risk of PC.72,73

A large prospective study in the United States (US) followed a cohort of 467,922 men and 588,321 women for 16 years who had no reported history of cancer. The results showed that independent of a high body mass, T2DM acts as a predictor of mortality from cancer of the colon, pancreas, female breast, male liver and bladder.74 Even though there is a strong association between PC and DM, the temporal sequence is unclear. However, 1% of newly diagnosed DM patients greater than 50 years of age will contract PC within three years.75

A population based retrospective cohort study in China showed that increased risk of developing cancer was found in both male and female T2DM patients with a standardized incidence ratio (SIR) of 1.331 (95% CI, 1.143-1.518) and 1.737 (1.478-1.997), respectively. As for different cancer subtypes, both male and female T2DM patients had a significantly increased risk of PC with the SIRs of 2.973 (1.73-4.21) and 2.687 (1.445-3.928), respectively. These findings indicated that patients with T2DM have an increased risk of developing PC.76

A systematic review of the association between DM and PC was undertaken by searching electronic databases and journal references from 1973 to 2013 in Australia. A total of 88
Biadgo B and Abebe M. Association between Type 2 DM and Pancreatic Carcinogenesis

independent studies, including 50 cohort and 39 case control studies, were examined. The overall summary RR was 1.97 (95% CI, 1.78-2.18) with marked heterogeneity that could not be clearly attributed to any subgroup analyses. The risk of PC was greatest early after the diagnosis of DM and remained elevated long after the diagnosis. The individual level RR ranged from 6.69 at less than 1 year to 1.36 at 10 years.77,78

A prospective study found an association between a history of DM and subsequent risk of cancer in Japan. In men, a 27% increase in the risk of total cancer incidence (hazard ratio [HR] 1.27, 95% CI 1.14-1.42; and HR 1.85, 95% CI 1.07-3.20)78 was seen for PC alone with a history of DM. A study done by the Alpha-Tocopherol Beta-Carotene Cancer prevention study shows smoking had significant (two-fold) contribution, increasing the risk of PC carcinogenesis among male DM patients male smokers.79

Recent meta-analyses revealed an association between T2DM and cancer in Austria. The strongest relationship was demonstrated for liver and PC, followed by endometrial cancer. A study investigated cancer incidence in Tyrolean subjects with T2DM by linking the data from the DM and cancer registries, including 5,709 T2DM patients. Site-specific analyses revealed statistically significantly elevated SIRs for PC (1.78; 95% CI, 1.02-2.89) for women, and (1.87; 95% CI, 1.11-2.96) for men. Sub-analyses performed by time of DM diagnosis revealed that SIR was highest in the first year after DM diagnosis, but the SIR was higher for cancers in women more than five years after DM diagnosis.80

A study of the association between T2DM and the risk of PC adenocarcinoma in pooled data from the National Cancer Institute PC cohort consortium in USA included 1,621 pancreatic adenocarcinoma cases and 1,719 matched controls from 12 cohorts using a nested case-control study design. The results show that self-reported DM was associated with a 40% increased risk of PC (OR, 1.40; 95% CI, 1.07-1.84). The association differed by duration of DM. The risk was highest for those with a duration of two to eight years (OR, 1.79; 95% CI, 1.25-2.55). There was no association for those with nine and above years of DM (OR, 1.02; 95% CI, 0.68-1.52). The findings of the study provide support for a relationship between DM and PC risk. The absence of association in those with the longest duration of DM may reflect hypoinsulinemia and warrants further investigation.81 Metformin may have a protective effect on the development of PC.15

A hospital-based case-control study at University of Texas M. D. Anderson Cancer Center, USA was conducted from 2004 to 2008 enrolling 973 patients with pancreatic adenocarcinoma, including 259 DM and 863 controls, 109 of whom were diabetics. DM patients who had taken metformin had a significantly lower risk of PC compared to those who had not taken metformin, with adjustments for potential confounders. This difference remained statistically significant when the analysis was restricted to patients with a duration of diabetes over two years or those who never used insulin. In contrast, diabetic patients who had taken insulin or insulin secretagogues had a significantly higher risk of PC compared to DM patients who had not taken these drugs.12

A meta-analysis of 9,220 individuals with PC in 36 studies published between 1966 to 2005 included 17 case-control and 19 cohort studies. The combined summary OR was 1.82, 95% CI 1.66-1.89, with evidence of heterogeneity across the studies (p<0.002 for case control and p<0.05 for cohort studies) that was explained, in part, by higher risks being reported by smaller studies.16

The complex relationship between the diseases has been the subject of numerous clinical, epidemiological, and experimental studies. Epidemiologic studies have suggested that long-standing T2DM is a modest risk factor for the development of PC. Meta-analysis of multiple cohort and case control studies shows that the risk of PC in patients who have had DM for more than 5 years is 1.5- to 2-fold higher than recently diagnosed DM cases.82 In a recent meta-analysis of 20 publications, comprising 13,008 cancer patients with concurrent T2DM, researchers found that patients treated with metformin had better overall and cancer-specific survival than those treated with other types of glucose lowering agents.83 A meta-analysis of three studies, in which 2,192 PC patients were compared with 5,113 controls, revealed a 1.8-fold increase in risk of PC associated with T2DM.84

A population-based retrospective cohort study from British Columbia, Canada linked health databases found a significantly increased risk of PC within three months following DM onset.85 Another study showed an increased risk of developing PC in patients with T2DM among randomly selected patients in the San Francisco Bay Area.86 Finally, a cohort study in USA comparing 110,919 DM subjects and 211,695 controls provides strong support for an etiological role of
T2DM and hyperinsulinemia in the pathogenesis of PC.\textsuperscript{87}

4. Association between duration of type 2 diabetes mellitus and the risk of pancreatic cancer

The development of DM within a few years of a PC diagnosis suggests an effect of the tumor, whereas DM of longer duration is more likely to contribute to the development of PC.\textsuperscript{14} In many studies, an association between long-standing DM and an increased rate of death from PC was observed. Controversies also exist regarding the association of long-standing DM and PC; some epidemiological studies refute the possibility that long-standing DM is a risk factor for PC.\textsuperscript{88-90} However, a similar study in the USA reported that long-standing DM increases the risk of PC by 40% to 100%.\textsuperscript{84} Moreover, a review of studies examining the association between T2DM and PC suggests that long-standing DM is an etiologic factor for PC; new onset is its manifestation. There is a modestly elevated risk of PC among persons with long-standing DM.\textsuperscript{83}

In contrast, recent onset T2DM is associated with a four to seven-fold increase in risk of PC, such that 1% to 2% of patients with recent onset DM will develop PC within three years.\textsuperscript{91} Using data from the General Practice Research Database, a study in 2012 showed that DM was associated with an increased risk of PC but the risk is to newly diagnosed DM of less than two years.\textsuperscript{92} DM individuals who had been diagnosed less than four years prior had a 50% greater risk of developing malignancy compared with individuals who had DM for over four years. These results support a strong causal association between recent T2DM and PC.\textsuperscript{16,77} This is in contrast to other findings that long-standing DM has higher risk of developing PC than short-term T2DM.

**CONCLUSION**

This review finds that T2DM and PC are common health problems, and an association between these diseases was demonstrated by several epidemiological studies. The relationships between PC and alterations in glucose metabolism are very complex. In many studies, an association between long-standing T2DM and an increased rate of subsequent death from PC was indicated, but controversies exist. Some epidemiological studies have excluded the possibility that long-standing DM is a risk factor for PC; rather recent onset contributed more to carcinogenesis. Some studies showed evidence that longstanding diabetes is an etiologic factor for PC, while new onset diabetes is its manifestation, but still there is discrepancy in the literature. The main finding of this review were that metformin has a protective effect on the development of PC and long term duration of DM was not a risk factor for PC. Most research reported that recent-onset diabetes was associated with increased risk for PC. In conclusion, it is believed that T2DM, duration of diabetes are risk factor for pancreatic carcinogenesis and there is metabolic link between the diseases.

**RECOMMENDATION**

In summary, the finding of the review recommends early detection and screening of new onset T2DM patient for PC should be employed in the management of patients with T2DM. Understanding the mechanisms of the relationship between DM and PC is important for improving long-term survival, and opens research opportunities for the development of novel preventive and therapeutic strategies. In addition, future studies should focus on understanding the pathogenesis of T2DM-associated PC and identifying biomarkers that can distinguish whether the cancer is T2DM associated or any other causes of PC carcinogenesis.

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