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REVIEW

Diabetes and pancreatic cancer: Exploring the two-way traffic

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Abstract

Pancreatic cancer (PC) is often associated with a poor prognosis. Long-standing diabetes mellitus is considered as an important risk factor for its development. This risk can be modified by the use of certain antidiabetic medications. On the other hand, new-onset diabetes can signal towards an underlying PC in the elderly population. Recently, several attempts have been made to develop an effective clinical tool for PC screening using a combination of history of new-onset diabetes and several other clinical and biochemical markers. On the contrary, diabetes affects the survival after treatment for PC. We describe this intimate and complex two-way relationship of diabetes and PC in this review by exploring the underlying pathogenesis.

Key Words: Chronic pancreatitis; Diabetes; New onset diabetes; Pancreatic adenocarcinoma; Pancreatic cancer; Type 3c diabetes

Core Tip: Type 2 diabetes mellitus can increase the risk of pancreatic cancer (PC) and certain antidiabetic medications can modify this risk. New onset diabetes in

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combination with other clinical and biochemical markers can serve as an effective screening tool for PC. On the contrary, the glycaemic status affects the treatment outcome of PC. More awareness among clinicians is required about the two-way relationship between diabetes mellitus and PC.

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INTRODUCTION

Pancreatic cancer (PC) is one of the few malignancies associated with a dismal prognosis. Its incidence is on the rise and is one of the leading causes of cancer-related death worldwide[1]. Similarly, type 2 diabetes mellitus (T2DM) accounts for a significant morbidity and mortality owing to a global increase in its incidence. Its prevalence is predicted to reach up to 700 million by 2045[2]. Longstanding diabetes has been regarded as a modest risk factor for PC. On the other hand, new-onset diabetes mellitus (NOD), especially after the 5th decade of life is often observed as a harbinger of an underlying PC. There is also a simultaneous increase in obesity worldwide, which plays a key role in development of both T2DM and PC[3]. Thus, this surge in diabetes and obesity prevalence may eventually increase the risk of PC in a significant number of population in near future[4].

Diabetes and PC have a multifaceted relationship. There are different types of diabetes as per the American Diabetes Association but two types of diabetes, namely T2DM and type 3c diabetes, merit attention in relation to PC[5]. T2DM is a chronic non-communicable disease characterised by hyperglycaemia resulting from the defective insulin secretion due to progressive beta cell dysfunction in the face of ongoing insulin resistance (IR)[5]. The diabetes associated with different exocrine pancreatic disorders is known as type 3c diabetes. The duration of DM has an important relationship with development of PC. However, the time duration cut-offs to define different types of diabetes are arbitrary and are varied. The time duration taken to define NOD in the context of PC is between 2-3 years[6]. On the contrary, when the diabetes is present for more than 2-3 years before the diagnosis of PC, it is considered as a long-standing T2DM. However, differentiating between this two entities is very difficult in a given subject of PC, since many patients of T2DM have a long asymptomatic undiagnosed period[5].

T2DM can have an impact on the outcome of different treatment modalities of the PC. Moreover, different drugs used for treating T2DM can affect the risk of PC as well. Metformin has gained particular attention in this context. In the appropriate clinical context, a recent worsening glycaemic profile requiring insulin might point towards the development of PC in the elderly diabetes subjects. The main obstacle in the diagnosis of PC in DM is to identify the candidates to be screened as routine evaluation for PC is not recommended in them. Ongoing research in identifying the screening population based on clinical characteristics and biomarkers and developing different models based on the combination of such parameters continues. In this background, we aim to review the current literature for unfolding the complex but intricate relationship between diabetes and PC.

SEARCH STRATEGY

The PubMed search was carried out for relevant articles by three authors (AR, JS, PM). The references of the pertinent articles were also searched for additional appropriate studies. The keywords and combinations included in the search were: 'diabetes'; 'new onset diabetes'; 'pancreatic cancer-related diabetes'; 'pancreatic cancer' and 'diabetes'; 'new onset diabetes' and 'pancreatic cancer'; 'long term diabetes' and 'pancreatic cancer'; 'pancreatic ductal adenocarcinoma' and 'diabetes'; 'metformin' and 'pancreatic cancer' and 'diabetes'; 'Type 3c diabetes' and 'pancreatic cancer'. The

search was restricted to only English literature and predominantly focused on the recent evidence. The appropriate articles to be included in this review were selected by SK, DN and RK.

RISK OF PC IN LONG-STANDING DIABETES MELLITUS

The evidence of association between NOD and the PC is consistent (see below); however, the evidence for risk of development of pancreatic ductal adenocarcinoma (PDAC) in long-standing diabetes is mixed. PDAC is the most common form of PC. Moreover, the risk is cumulative and is in continuum with the fasting blood glucose levels and the risk consistently increases from normal glucose tolerance to prediabetes to diabetes[7].

The increased risk of PC in long-standing T2DM has been suggested across different population of the world, including Asians[8-10]. A recent report involving a large population (n = 112818 females and 46207 males respectively) over 30 years of cumulative exposure showed an increased risk of PDAC with long-standing diabetes over time (age-adjusted hazard ratio [HR] 2.16 [95%CI: 1.78-2.60])[11]. Another recently published meta-analysis also suggested an increased PC related mortality with T2DM (relative risk [RR] 1.67; [95%CI: 1.30-2.14])[12].

The summary of the evidence suggests that the reported RR for developing PDAC in long-term diabetes is modest and varies between 1.4-2.1[8,13]. The risk may persist even after adjustment for obesity and smoking, two important and independent risk factors for PDAC[14]. Additionally, PDAC risk is significantly more in NOD and although the risk reduces subsequently, it may remain significant as the duration of the diabetes gets longer as per few meta-analysis[13,15]. However, a 2015 summary review of the available meta-analysis questioned the robustness of diabetes and PDAC association[16]. Importantly, other population based studies did not find any association between long-standing diabetes and the development of PDAC[17,18]. Thus, the elevated risk of PC in long-standing T2DM is confounded by the factor that may originate from a common soil of obesity and IR. Further, the role of different anti-diabetic medications as a risk modifier cannot be ignored while assessing the risk.

The Mendelian randomization (MR) studies looking into causal association between long-standing diabetes and PC have yielded conflicting results. While some studies showed causal association, others did not[19,20]. A pooled analysis performed on MR studies including 8374 PC patients by Yuan *et al*[21], found an odds ratio (OR) of 1.08 (95%CI: 1.02-1.14; P = 0.009) for this association. Although this evidence suggests a modest increase in the risk of PDAC in long-standing T2DM, more studies are required to confirm this association in future.

RISK OF PC IN TYPE 3C DIABETES

Chronic pancreatitis is defined as the chronic progressive inflammation and fibrosis of the pancreas caused by various aetiology and finally results in both endocrine and exocrine pancreatic dysfunction[22]. Diabetes is found in 35%-50% of subjects with CP in the observational studies[23-25] and the prevalence of DM increases with the increasing duration of CP and may reach up to 90%[25]. This type of diabetes is known as type 3c diabetes. Diabetes is more common in patients with pancreatic calcifications, pancreatic exocrine insufficiency and those who underwent surgery[23,24]. In a meta-analysis including fifteen studies (8970 patients), the incidence of DM was 30% and the prevalence increased after 5 years of CP diagnosis[26]. Diabetes in CP is often difficult to manage as a significant proportion of subjects require insulin therapy[23]. Importantly, CP itself is a risk factor for the development of PC. Kirkegård *et al*[27] had shown the risk of PC in CP varies with the duration of the disease and the effect estimates were 16.16, 7.90 and 3.53 at 2, 5 and 9 years after the diagnosis of CP, respectively. Another important entity is fibro-calculous pancreatic diabetes (FCPD), also known as tropical calcific pancreatitis, a relatively common cause of type 3c diabetes in certain tropical countries. FCPD also carries a very high risk for the development of PDAC[28].

Thus, it is important to look for CP in a given patient of diabetes and a closer follow-up with appropriate imaging is needed for diagnosis of PC in suspected cases. Since CP patients are often malnourished, progressive weight loss or anorexia despite adequate glycaemic control should alert the clinician for the possibility of PDAC.

RISK OF PC IN NEW-ONSET DIABETES

NOD has been considered as an important metabolic marker for the development of PDAC within the first 2-3 years of its diagnosis. NOD serves as a harbinger of PDAC in patients more than 45-50 years of age and hence calls for a careful follow up[29-31]. An earlier study demonstrated a 0.85% chance of development of PC within 3 years of diagnosis of diabetes in persons aged 50 years or more[32]. This study also showed that the risk was almost 8 times higher in patients with NOD. In a large cohort of 2.3 million Israeli population, a very high risk for developing PC was observed both in women and men (HR of 15.24 and 13.88 respectively) during the first year after the diagnosis of diabetes[33]. Two meta-analyses[13,14] also showed a 5-7 times elevated risk of PDAC in NOD, particularly within first year of diagnosis. Such an association was confirmed in different ethnicities like African Americans, Latinos[34] and Asians [35].

Agarwal *et al*[36] reported a very high prevalence of DM (68 %) in patients with PC compared to age matched other cancers subjects or non-cancer controls. Similarly, the number of NOD within the preceding 36 mo was markedly higher in PC than the other two groups (40% *vs* 3.3% *vs* 5.7%). About 50%-74% of the PC related diabetes is of recent onset (< 2-3 years duration)[6,37]. The prevalence of dysglycaemia in PDAC was more when standard oral glucose tolerance test (OGTT) was used instead of fasting glucose levels for diagnosis (78% *vs* 45%)[36,38]. The abnormalities in glucose metabolism are frequently missed in PDAC. The importance of making a preoperative diagnosis of glucose abnormality needs to be emphasized in this setting as it is shown to influence the surgical policy in up to 15% of patients[39].

It was also observed that a significant proportion of NOD in patients with PDAC resolved after pancreatic resection[37]. This indicates that PDAC by itself is causally related to the development of NOD, which is an early and specific biomarker for PDAC rather than a mere consequence. Besides the NOD, a deterioration of the existing glycaemic control in the form of elevated glycated hemoglobin **(**HbA1c) has also been associated with the development of PDAC[38].

MECHANISM OF DEVELOPMENT OF PC IN LONG-STANDING T2DM

The potential mechanism responsible for the development of PDAC in long-standing diabetes is poorly understood (Figure 1). The proposed theories are: (1) IR and the resulting direct effect of hyperinsulinemia[40]. A very recent study performed in a large prospective cohort (> 0.5 million subjects with a median follow-up of 8.4 years) has shown that higher IR as assessed by homeostatic model assessment- IR (HOMA-IR) is an important and independent risk factor for PC related mortality even in patients without diabetes[41]; (2) Cancer promoting role of the IGFs[42]; (3) The potential role of hyperglycaemia itself to alter several biochemical pathways involved in the carcinogenesis; (4) The synergistic effect of obesity and inflammation ('the common soil hypothesis'); and finally (5) Genetic predisposition to both these conditions. Experimental evidence is emerging to explain the molecular mechanism linking T2DM and PDAC. They include the roles of cellular senescence promoted by both T2DM and obesity[43], advanced glycation end products and its receptor[44], metabolic reprogramming by hyperglycaemia[45] and the interplay between non-alcoholic fatty pancreas development in the milieu of obesity and diabetes[46].

MECHANISM OF DEVELOPMENT OF NOD IN PC

PDAC by itself induces a potential 'diabetogenic' state. PC-associated NOD is grouped under Type 3c diabetes, which also includes diabetes caused by CP[47]. The mechanisms linking PC and NOD are shown in Figure 2. The hypothesis that NOD is the result of destruction of the endocrine pancreas by PDAC is not a plausible explanation because NOD can be present even before PC becomes radiologically detectable[48] and has also been shown to improve after surgery[37]. Hence, it is essential to search for systemic mediators of NOD in PC; until now, only a few of them have been substantiated.

Role of insulin resistance

Initial pioneering studies have shown that PC-associated NOD causes marked impairment in insulin action[49-51], more profound in patients who had diabetes[50].

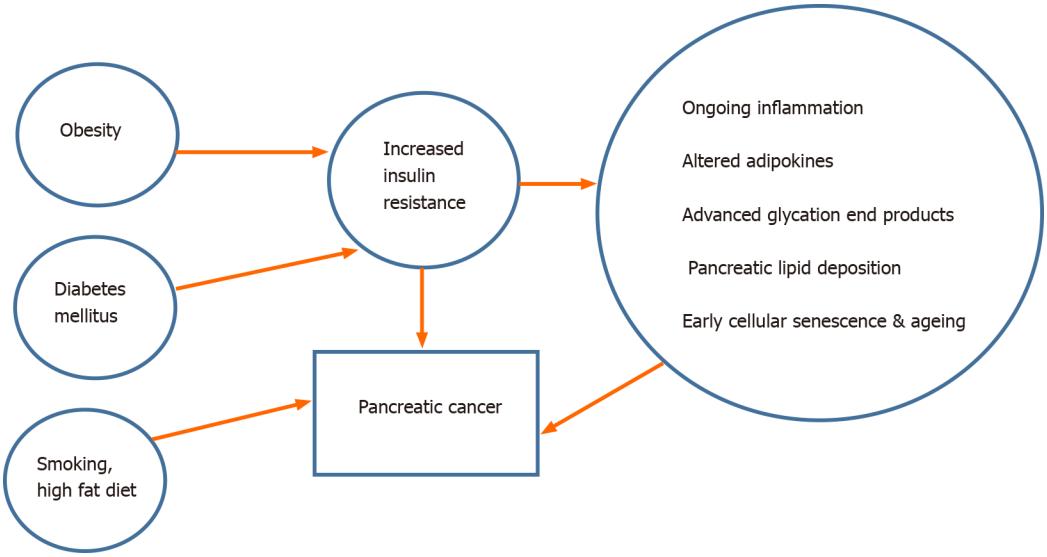

Figure 1 Schematic diagram depicting the interplay of various proposed factors leading to development of pancreatic cancer in long-standing diabetes mellitus.

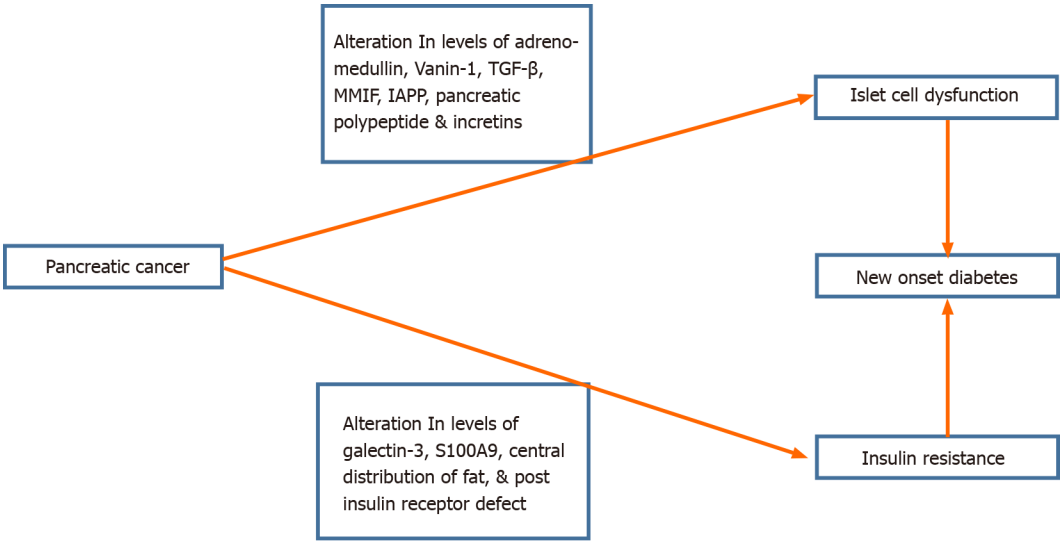

Figure 2 Schematic diagram for the possible mechanism for the pathogenesis of new-onset diabetes mellitus in pancreatic cancer. IAPP: Islet amyloid polypeptide; MMIF: Macrophage migratory inhibiting factor; TGF-β: Transforming growth factor-beta.

Insulin mediated glucose entry at the level of skeletal muscle was particularly found to be impaired significantly[52]. Interestingly, Permert *et al*[49] also demonstrated an improvement in whole body insulin sensitivity following surgery by using a hyperglycaemic clamp, which is considered to be the gold standard in evaluation of insulin sensitivity.

Thus, IR is an important determinant of the PDAC-related NOD, but the underlying mechanisms remain to be further studied. Currently available studies have suggested that IR may be related to the post-insulin receptor defect, particularly involving glycogen synthesis and storage pathways[53]. Recent experimental studies have found that PDAC-associated exosomes can inhibit the insulin receptor signalling pathway downstream of the receptor causing IR in skeletal muscle[54]. Another proteomic study revealed that galectin-3 and S100A9, which are overexpressed in PDAC-related NOD, can induce IR and can also serve as markers in distinguishing this entity from T2DM[55].

The role of islet amyloid polypeptide (IAPP) in the development of IR was initially suspected but later its clinical utility was not proven[56]. It was also suggested that PDAC-related NOD is due to the differential effect of ectopic fat as PDAC is characterized by subcutaneous fat loss and preservation of visceral fat[57]. However, a recent

study found that 30-18 mo before the diagnosis of PDAC, a significant proportion of patients had developed hyperglycaemia without any discernible change in the muscle or fat compartments[58,59].

Role of islet cell dysfunction

Pancreatic islet cell dysfunction is likely to be a crucial factor in the development of PDAC-related NOD. The morphology of the pancreatic islet in PC was recently characterized by Nagpal *et al*[60]. They demonstrated a significant reduction in islet density, beta and alpha cell area in PC compared to T2DM/control subjects. PC-related DM had lower IAPP deposition than T2DM. The lower IAPP deposit in PC related DM was also noted in an earlier study[61]. Future studies should explore the functional impact of such morphological changes.

Earlier studies have demonstrated a lower C-peptide response to glucagon stimulation suggestive of a beta cell secretory dysfunction in PDAC[62]. Beta cell function as assessed by HOMA-B was also found to be lower in PDAC patients with higher fasting glucose and diabetes[63]. In experimental studies, it was shown that beta cell in PDAC secrete increased amount of amylin preferentially while insulin secretion is diminished[64-66].

There is an experimental evidence for inhibition of insulin secretory function of the beta cell by adrenomedullin, which is released from PC-associated exosomes[67]. The role of adrenomedullin inhibiting beta cell insulin secretion in response to glucose was previously shown[68]. Moreover, adrenomedullin upregulation was noted in PC and its role in IR was also demonstrated[68]. Adrenomedullin was found to be a mediator for the increase in the exosome-induced lipolysis of the subcutaneous fat in PDAC [69]. The role of adrenomedullin as a screening biomarker is currently investigated in a prospective cohort study to identify patients with NOD and underlying PDAC[70].

Vanin-1 helps in hydrolysis of pantetheine and synthesis of vitamin B5 and cysteamine, which are required for lipid, energy and coenzyme A metabolism[71]. The role of vanin-1 is implicated in PDAC-induced paraneoplastic islet cell dysfunction, predominantly mediated by decreasing glutathione and elevating oxidative stress[72]. The same group earlier identified vanin-1 as a distinct marker of PDAC-related DM based on gene expression profile of the peripheral blood[73]. The role of transforming growth factor-beta (TGF-β) in the destruction of pancreatic beta cell had also been shown in animal studies[74,75] The macrophage migratory inhibiting factor was overexpressed in PDAC and was shown to decrease the beta cell secretory function [76].

A recent study has demonstrated that the markers of beta cell de-differentiations are consistently higher in non-diabetic PDAC patients suggesting the possible role of beta cell reprogramming in the early beta cell dysfunction even before the appearance of hyperglycaemia[77]. This dedifferentiation might be potentiated by the inflammatory milieu triggered by the PDAC.

Studies relating to alpha-cell function with PDAC-related DM are lacking. One study showed a higher glucagon/insulin ratio as a marker of NOD in PDAC[78]. Another small study revealed hyperglucagonemia in PDAC-related DM patients[79]. However, further studies are required to delineate the role of alpha cell dysfunction in PDAC-related diabetes.

Pancreatic polypeptide (PP) is released from the PP cells predominantly located in the head of the pancreas. PP cells have an important paracrine action including suppressive effect on glucagon secretion from alpha cell. Interestingly, one study had reported diminished PP response at 30 min following a mixed meal challenge in PC-related DM patients as compared to T2DM[80]. This was seen in tumours located in the ventral part of the pancreas. However, another study did not find any difference in fasting PP levels between PDAC-related DM, CP and T2DM[81]. Further studies should explore the role of PP in NOD and its use as an effective screening tool for PDAC.

Very few studies have evaluated the role of incretin hormones in the pathogenesis of PDAC-related DM. Interestingly, one study reported a lower gastric inhibitory polypeptide (GIP) and PP secretion in PDAC patients with diabetes as compared with T2DM patients, without any difference in glucagon-like peptide 1 (GLP-1) response [82]. Importantly, those with NOD or prediabetes with weight loss (> 2 kg) had significantly lower GIP. However, further studies are required to confirm this association. In-vitro studies had demonstrated that a lower GIP and GLP-1 response might be related to the inhibitory effect of the PDAC-exosomes on the proprotein convertase subtilisin/kexin type 1/3 enzyme which is responsible for cleaving the pro-glucagon molecule to generate the incretin peptides[83]. This study suggested the possibility of pancreatic exosome mediated dysfunction of the incretin hormones in

the gut.

EARLY DETECTION AND/OR SCREENING MODELS FOR PC IN DM

Clinical indicators

Till now, the recommendations regarding systemic screening of a person with diabetes to identify PDAC are not standardized. But, whom to screen and how to screen is not defined clearly by any guidelines till now to the best of our knowledge. So, it is necessary to develop a screening tool based on NOD and other risk factors. Since the yield of screening in such population is low, whether systematic screening is cost-effective and practically feasible remains an area of active debate.

The screening of patients with diabetes for PC is based on filtering of diabetes patients based on presence of associated clinical factors or level of biomarkers or a combination of such factors. NOD within 3 years of diagnosis increases the risk of PDAC 6-8 times more than the general population, but the prevalence of PDAC in such circumstances is low (0.8%-1%)[32].

It is a challenge to differentiate PC induced NOD from the more commonly encountered T2DM based on clinical and biochemical factors in clinical practice (Table 1). There are many overlaps between these two entities[84-86]. Munigala *et al* [87], identified age ≥ 65 years, heavy smoking, non-obese status at diagnosis, history of CP or gallstones as different risk factors of PC in a prospective cohort of NOD. One study reported a 40% higher risk of PC in patients with dyslipidaemia, although the association with specific lipid parameter was not mentioned[88].

Two other important factors that may provide a clinical clue for PC associated NOD are weight loss and worsening of hyperglycaemia. A continued weight loss in the presence of NOD was observed in a greater number of PC patients (59% *vs* 30%) than T2DM[89,90]. The amount of weight loss was also more in PC patients (8.3 ± 8.3 kg *vs* 0.8 ± 4.8 kg). Mueller *et al*[91] showed that weight loss of more than 10% had an adjusted OR of 3.58 (95%CI: 2.31-5.54) for development of PC. The presence of weight loss of more than 15% was not only associated with an increased odds of PC in NOD [91] but also in patients with long-standing diabetes[92]. Olson and colleagues showed that NOD and severe weight loss often occurred together before the diagnosis of PC [90]. Chen *et al*[11] observed that in a subject with NOD, when weight loss was unintentional or occurred in an individual with body mass index (BMI) less than 25 kg/m^2, then it substantially increased the risk of PC. Hence, weight change should be actively sought in elderly diabetes and warrant further investigation for PC.

Sah *et al*[58] reported worsening of hyperglycaemia, in the 18 to 6 mo before the diagnosis of PDAC. Similarly, rapid elevation of both blood glucose and HbA1c was observed by Huang *et al*[93] in the months preceding the detection of PC. The worsening of hyperglycaemia more often required the use of insulin treatment[90]. Thus, rapid deterioration of glycaemic control should alert a physician to screen for PDAC.

Another important feature is the loss of muscle mass, which is also known as sarcopenia. Sah *et al*[58] observed loss of subcutaneous adipose tissue even 6 mo before PDAC diagnosis. It was suggested that the preferential loss of subcutaneous adipose depot with relative preservation of the visceral adipose tissue might explain the IR and the worsening of glycaemic status[57]. However, a recent study did not find any difference in the prevalence of cachexia, skeletal muscle loss or weight loss between PC patients with or without DM[59]. Overall, sarcopenia suggests advanced disease and often portend poor survival, but its relationship with diabetes development need to be assessed in future studies[94].

Screening models

Interestingly, another upcoming approach is the development of a predictive model based on easily available clinical features in NOD. This model can identify NOD patients to be screened for PC and thus improve the detection rate while significantly decreasing the cost[30]. Sharma *et al*[95] came up with a model known as the Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC). This is a risk prediction model based on three different factors: change in weight, change in blood glucose, and age at the onset of DM. A score of 3 or more identified 78% of patients (n = 7/9) with 85% specificity. In the initial model, a score of more than 3 predicted a significantly increased risk of PDAC (4.4-fold) and a low END-PAC score of less than 0 had a very low risk of development of PDAC. This model was further assessed in a retrospective cohort of NOD patients (n = 13947) and 2% of high risk population (62 out of 3038)

Table 1 Factors that can help in differentiating pancreatic cancer associated new onset diabetes from type 2 diabetes mellitus

Clinical indicators	Biochemical markers
Age > 65 yr	Carbohydrate antigen 19-9
Heavy smoker	Galectin 3
Low body mass index	S100A9
History of chronic pancreatitis or gall stone disease	Insulin like growth factor-1
Recent worsening of hyperglycemia in an elderly patient	Osteoprotegerin
Weight loss associated with diabetes onset	Pancreatic polypeptide
Loss of subcutaneous fat and muscle mass in imaging studies like dual energy X-ray absorptiometry or magnetic resonance imaging	Thrombospondins- 1
	Vanin 1
	Matrix metalloproteinase-9
	MicroRNAs

were diagnosed with PDAC within 3 years yielding a sensitivity and specificity of 63% and 78% respectively at the score level of 3 or higher[96]. The positive predictive value (PPV) and negative predictive value were 2.0% and 99.7%, respectively. Another model was proposed by Boursi *et al*[97] based on The Health Improvement Network, which is a large primary care electronic research database from the United Kingdom. This prediction model included several easily available clinical parameters like age, BMI, change in BMI, presence or absence of smoking, use of proton pump inhibitors and other anti-diabetic medication including metformin. The laboratory parameters include levels of hemoglobin, creatinine, and alkaline phosphatase, HbA1c and cholesterol. The area under the curve (AUC) for the final model was 0.82 (95%CI: 0.75–0.89) and at a risk threshold of 1% for screening for PDAC, around 6% of patient with NOD would have to undergo systemic screening. The sensitivity, specificity and PPV at this level were 44.7%, 94.0% and 2.6%, respectively. Thus, though these model systems are encouraging and can narrow down on the screening population, they are limited by poor sensitivity and lower PPV[30] and further improvement is required before routine clinical use. Recently, a protocol of a multicentric, prospective observational study (NODES Trial) has been published, which intends to follow up new-onset (≤ 6 mo) diabetes patients over 60 years of age with both clinical and valid biomarkers [98]. The study also aims to evaluate for biomarkers that can distinguish patients with PDAC more precisely. Such studies will be invaluable in understanding and defining a screening protocol in NOD patients to identify PDAC as early as possible.

BIOMARKERS IN THE SCREENING OF PC IN DM

The role of different biomarkers in assisting the early diagnosis of PC among DM patients is crucial. A plethora of studies on different biomarkers have been published in the literature, though till now, none of them have reached the routine clinical use. The search for an easy-to-use clinically useful and cost-effective marker is still ongoing. Finding of suitable biomarkers is a difficult task in a relatively uncommon disease like PC and moreover, presence of diabetes can confound the measurements of different biomarkers in such setting[30]. A detailed discussion on this topic is out of the purview of this article, but a brief description on the latest biomarkers are discussed here. The proposed biomarkers are either measured in the blood or tissue fluids and they are the result of the 'multi-omics' studies involving proteomics, genomics and metabolomics.

Hormones involved in glucose homeostasis

The biomarkers, which draws our attention first is the biomarkers related to the glucose metabolism. Sharma *et al*[99] have shown that rising fasting plasma glucose itself predates the development of PDAC (36-60 mo before PDAC diagnosis) and is often related to the size of the tumour. Though fasting blood glucose levels increased concordantly with the volume of the tumour, no such relationship with the tumour gradation was reported. Another study reported a higher serum glucagon/insulin

ratio with a cut-off of 7.4 ng/mIU could differentiate PC induced NOD from T2DM with 77% sensitivity and 69% specificity[78]. A study demonstrated a higher glucose stimulated glucagon in PC patients with DM, suggesting glucagon as a potential biomarker[79].

Incretins involved in glucose homeostasis

The role of different gut polypeptides involved in the glucose homeostasis was also studied in PDAC patients. It was found that a significantly lower plasma concentrations of GIP and PP in patients with PC irrespective of the degree of glucose intolerance as compared to the T2DM and normal healthy controls[82]. A diminished PP response to a mixed meal was also observed earlier in PDAC associated diabetes in a small study[80]. However, another study could not find a difference in fasting PP levels between PDAC patients with or without diabetes and T2DM[81]. Thus the blunted PP response in PDAC can serve as an important tool for screening for PDAC, but the time-line is not well established and studies with a larger sample size may further consolidate PP as an important biomarker.

Carbohydrate antigen 19-9

A study by Choe *et al*[100] has shown that in asymptomatic NOD patients, a higher carbohydrate antigen 19-9 (CA19-9) levels above the upper normal limit had a 5.5 times risk of developing PC within 2 years of diagnosis. Another retrospective analysis showed similar results and found that the odds for development of PC in NOD patients with elevated CA19-9 was consistently higher, particularly in patients with elevated bilirubin levels[101]. Murakami *et al*[102] proposed that a cut-off of serum CA19-9 level of 75 U/mL can discriminate between patients with diabetes with or without PC. At this cut off, the sensitivity and specificity of CA19-9 for PC was 69.5% and 98.2%, respectively, while the AUC was 0.875 (95%CI: 0.826-0.924). A combination of elevated CA19-9 and carcinoembryonic antigen was also shown to detect PC among DM patients[103]. However, it is important to note that the utility of CA19-9 may be limited by the fact that it is affected by the levels of glycemia. CA19-9 levels must be interpreted in the context of ongoing glycaemic control and patients with diabetes per se may have elevated CA19-9[104].Thus there is a need to optimize the CA19-9 cut off level in DM patients for PC detection.

Thrombospondin -1

Another promising biomarker is thrombospondin-1 (TSP-1), a multimeric protein with anti-angiogenic properties. TSP-1 levels were found to be lower in PDAC patients, particularly those with diabetes as compared to non-diabetes and this lower levels were detected even 24 mo before the diagnosis of PDAC[105]. According to this study, TSP-1 levels in combination with CA19-9 yielded an AUC 0.86 in the detection of PDAC. Importantly, a lower TSP-1 levels were also noted in PDAC associated diabetes but not in the long-standing T2DM.

Vanin-1 and matrix metalloproteinase 9

Vanin-1, a protein involved in the oxidative stress pathway was found to be associated with paraneoplastic islet cell dysfunction (see earlier) and can serve as a potential biomarker in detecting PC among DM patients. Huang *et al*[73] have shown that the levels of *Vanin-1* genes were significantly upregulated in PDAC and an elevated levels of both vanin-1 and matrix metalloproteinase 9 (MMP9) in serum using quantitative real-time polymerase chain reaction could differentiate PDAC associated diabetes from T2DM. The AUC for the combination of both Vanin-1 and MMP9 was 0.950 with a sensitivity of 95% but the specificity of 76%. A combination of CA19-9 and MMP9 was also found to be helpful in discriminating PDAC-related diabetes from T2DM with an AUC of 0.886[106].

Galectin-3 and S100A9

Galectin-3 is a β-galactoside–binding lectin involved in the proliferation, migration and invasion of PC cells[107] whereas S100A9 protein is involved in the inflammation through toll-like receptor-4[108]. Liao *et al*[55] have shown that levels of both galectin-3 and S100A9 were higher in PDAC related DM than T2DM. They also found that the serum levels of both galectin-3 and S100A9 proteins can differentiate between PDAC related DM and T2DM with the AUC of 0.83 (95%CI: 0.74–0.92) and 0.77 (95%CI: 0.67–0.87) respectively.

MicroRNAs

Alteration in the profile of serum microRNAs (miRNAs) have been postulated as important biomarkers in recent times. One study reported that a panel of six miRNAs (miR-483-5p, miR-19a, miR-29a, miR-20a, miR-24, miR-25) could differentiate between PDAC related DM and T2DM[109]. The AUC for the differentiation of these two entities was 0.885 (95%CI: 0.784-0.986). However, the micro RNA profiles (miR-192, miR-196, miR-200, miR-21, miR-30 and miR-423) were found to be similar in PC patients with or without DM in a study by Skrha *et al*[110]. This list of miRNAs will be increasing in the future but the potential ones should come out from the prospective follow-up studies of the NOD patients.

Metabolomics

Studies have used extensive metabolomics approach either through liquid or gas chromatography and mass spectrometry or nuclear magnetic resonance imaging technique to identify various metabolites in order to identify specific biomarkers that can differentiate between PDAC-related DM and T2DM. One study revealed a distinct signature of 62 different serum metabolomes in PC related DM as compared to T2DM [111]. Out of them, two metabolites namely N-Succinyl-L-diaminopimelic-acid and PE (18: 2) had shown good sensitivity (93.3%) and specificity (93.1%) for PC in the logistic regression analysis. A recent nuclear magnetic resonance based study also identified a panel of eight metabolites with good accuracy (more than 80%) in the discrimination of PC and long-standing T2DM patients[112]. In future, possibly a panel of metabolites will help us to improve the precision medicine in identifying the cases requiring close follow-up for detection of PC among diabetes patients.

Other new biomarkers

There have been several other biomarkers proposed for the differentiation of the PDAC associated diabetes from T2DM. A very recent analysis of several immune related proteins including cytokines, chemokines and adhesion molecules revealed that a panel of different molecules (GM-CSF, IL-31, RANTES, RESISTIN, FASL, & ICAM1) were different between PDAC related DM and T2DM with an AUC of 0.96 (0.93–1.00)[113]. This study paved a new way in the screening of PC in diabetes patients. The other tools that can be used to screen PC are plasma free amino acid index[114], combination of either neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio and CA19-9[115], angiopoietin-like protein 2[116] among others with reported variable AUC.

In summary, although a great numbers of promising biomarkers have been studied to detect PC early in diabetes patients, a very few have reached routine clinical use as of now. As more translational research is emerging, the main requirement of a panel of clinically useful biomarkers for early detection of PC in DM will be fulfilled in near future.

DIABETES AND THE TREATMENT OUTCOMES OF PC

Diabetes has an important role to play as a prognostic marker in PC patients. Pancreatectomy is the initial management strategy in PDAC. Currently, the evidence that diabetes may portend an unfavourable impact on the overall outcome of PC, particularly after surgery is not concrete[117]. Whether the treatment of the diabetes modifies this risk is also not clear at present. Hank *et al*[118] showed that diabetes subjects had a poor median overall survival (18 *vs* 34 mo; $P < 0.001$). Moreover, diabetes was associated with higher 30-d mortality (3.2% *vs* 0.8%; $P = 0.019$). Importantly, a larger tumour size, a greater number of lymph node involvement and more peri-neural invasion were seen in diabetes patients with PC. A negative association of diabetes with overall survival was also noted in a meta-analysis[119]. However there are studies which do not agree on such association[120,121], and rather showed paradoxical reduction in the risk of death[122]. A 2013 review showed that diabetes patients had a higher risk of post-operative complications (45% *vs* 35%)[123]. Baseline HbA1c more that 6.5%-7.0% was also found to be associated with a shorter survival[124,125].

Long-standing DM vs new onset DM

Although studies have shown a poor outcome in all diabetes patients, the relative role of duration of diabetes on PC outcome needs further clarification. Very few studies

have shown the stratified analysis based on diabetes duration. Long-standing diabetes was found to have an association with diminished survival in prospective studies [126]. This was also confirmed in a meta-analysis[127] involving 18 studies (16181 patients). Several other studies[117,128,129] did not find any significant effect of long-standing diabetes on the survival in PC. Jeon *et al*[117] reported impact of long-term diabetes on decreased survival in those with resectable PDAC (HR, 1.42; 95%CI: 1.13–1.78) but not in advanced disease suggesting a role of staging in the outcome. It is important to note that the association of diabetes with prognosis became non-significant in most of the studies, after adjusting confounders like age, gender, BMI, smoking status and staging of the disease[128]. The evidence that diabetes patients can have a relatively larger pancreatic tumour size is well established[118,121,130,131].

On the other hand, the evidence is more consistent for a poorer outcome associated with NOD. A 2017 meta-analysis showed that only NOD was associated with shorter survival but not long-standing DM[119]. Similarly, other studies found that only NOD was a significantly independent predictor of decreased survival[129,132]. Importantly, Lee *et al*[133] have shown that NOD carries a higher risk of recurrence after pancreatic resection and may be a factor responsible for the poorer outcome. In contrast Jeon *et al* [117] did not find any impact of NOD on survival. Another point to consider is that whether post-surgery improvement of NOD has any impact on outcome. Though a study reported increased survival in patients where diabetes was resolved following surgery[134], future studies should substantiate this finding.

Impact of DM on the outcome after chemotherapy

Studies assessing the impact of diabetes in PC patients receiving chemotherapy have shown that, a prior diabetes status might be associated with a higher risk of death. Kleef *et al*[130] demonstrated a higher mortality rate in diabetes patients receiving adjuvant chemotherapy [HR 1.19 (95%CI: 1.01-1.40)]. Similarly, Hank *et al*[118] showed that median overall survival was lower in diabetes patients who received neo-adjuvant chemotherapy as compared to non-DM patients (18 mo *vs* 54 mo; $P < 0.001$). Another study showed diabetes to further add to the poorer outcome in metastatic disease treated with gemcitabine[135]. A meta-analysis looking at the impact of diabetes on the outcome following chemotherapy in PC (1034 with DM and 3207 without DM) demonstrated a lower survival and higher risk of death after chemotherapy in DM patients[136]. A high preoperative HbA1c was also found to be associated with non-completion of adjuvant chemotherapy and a higher risk of metastasis[137]. Diabetes also affects the survival in very advanced PC patients receiving palliative chemotherapy[138].

The mechanism behind the poorer outcome in PC with diabetes is not certain. Diabetes is associated with larger tumour size and hence a higher tumour stage. Hyperglycaemia has been shown to hasten the tumour development *via* sterol regulatory element binding protein 1 pathway[139]. There is also suggestion for an alteration in the tumour microenvironment in the presence of an elevated blood glucose level. Indeed, experimental studies have shown that hyperglycaemia increases the metastatic ability of the PC through aggravated hypoxia[140] or by increasing the perineural invasion[141]. The role of glycaemic variability is also suggested as a risk factor for promoting local invasion and metastasis *via* the retinoic acid receptor beta-runt related transcription factor 3-type VI collagen alpha 1 chain pathway[142].

EFFECT OF PC TREATMENT ON DIABETES

There is a complex relationship existing between patients undergoing surgery for PC and their glycaemic status. Glycaemic control is expected to worsen following pancreatectomy considering a significant loss of beta cells. However this is not often observed in clinical practice, particularly in patients with NOD after surgery. Studies[143-146] have either shown a significant improvement in their glycaemic control (75%) or resolution of NOD (20%-65%) after pancreatic surgery. It has also been reported that resolution of preoperative NOD after pancreatectomy may be a sign of a favourable outcome[134]. NOD has also been described in 15%-20% of patients[143,145,146] after surgery. One study reported deterioration of the glycaemic control in up to 40% post-operatively[147],when formal tests like OGTT and *i.v.* glucagon stimulation test were used. In the meta-analysis by Beger *et al*[148], cumulative incidence of NOD was found to be 15.5% after pancreatico-duodenectomy for malignant pancreatic tumours. Hence, it is necessary to assess the glycaemic status after pancreatico-duodenectomy even in those with pre-operative normoglycemia to achieve a better metabolic control after the

surgery.

ANTI-DIABETIC MEDICATIONS AND PC

Since diabetic patients will be receiving several medications for controlling hyperglycaemia, it is important to consider their effects in the context of PC. There are many excellent reviews[149] already available in this regard and we highlight salient points based on the recent available evidence.

Metformin

Metformin has garnered a lot of interest in recent times due to its anti-cancer effect and PC is not an exception. Metformin is the first line drug of choice for treating T2DM. A plethora of studies have looked into the three key aspects of metformin and their role in PC. They are: (1) Metformin as a risk modifier of PC development in T2DM[150-152]; (2) Effect of metformin on the overall survival following therapy[153]; and (3) Metformin as an adjuvant therapy in diagnosed PC[154].

Studies regarding metformin treatment as a risk modifier of PC have yielded mixed results. While some studies have shown risk reduction of PC in metformin users[155], other studies did not find such a beneficial impact of metformin in PC risk reduction [156,157] and even reported an increased association risk in metformin users[151]. Though earlier pooled analysis[150] had shown a decreased risk of PC, the studies included in those analysis were mostly retrospective and met with the significant lead time bias. Another complicating issue regarding the risk estimation is that the long duration of diabetes already present is itself a potential risk for PC and the NOD heralding the onset of PC often complicates the scenario further. Therefore, recent studies with better statistical designs are warranted to establish the role of metformin in PC prevention in a concrete manner.

Animal studies have shown that metformin decreases the PC cell proliferation[158, 159], its invasiveness[160] and thereby reduces the metastatic potential of PDAC[161]. Studies have also shown that metformin has a sensitization effect on chemotherapy, particularly gemcitabine[161,162]. The inhibition of TGF-β pathway is one of the several underlying mechanisms proposed to explain these effects[75,160]. Considering this finding, metformin might be expected to have beneficial result in PC. However, the clinical studies performed to assess the benefits of metformin have shown conflicting results. While few studies have suggested the survival benefit of metformin in PC patients[163-165], two phase 2 randomized controlled trials (RCTs)[166,167], observational studies[168,169] and other meta-analysis[170] refuted such finding.

The benefits of metformin observed in some earlier studies may be attributed to the immortal time bias that is inherent to meta-analysis studies[171]. Indeed, a meta-analysis taking into the account of immortal time bias did not show any additional survival benefit of metformin in DM patients with PC[170]. According to this meta-analysis, the effect size of reduction in the risk of survival was exaggerated by 18%. Again, the null effect of metformin on survival shown by the two RCTs was also flawed by the fact that metformin treatment was started late in the disease course and metastasis has already happened, leaving a small room to assess for the effect of metformin on survival outcome[166,167]. For this reason, it is important to focus on this area with well-designed RCTs in an earlier stage, including both DM and non-DM population. Further evidence is required to recommend treatment with metformin in PDAC patients with concurrent DM. Mild hyperglycaemia with obesity in early stage PC patients may be an ideal indication to start metformin. In summary, the risk reduction of PC and the overall survival following metformin therapy are not observed in recent well designed studies with improved statistical analysis taking into consideration of immortal time bias. Future phase 3 RCTs will be helpful in this context, mainly in selected PC candidates[172].

Insulin and insulin secretagogue

Insulin has a definite role in the pathogenesis of PDAC as hyperinsulinemia and IR are important risk factors for the development of PDAC (see above). Whether clinical use of insulin has any impact on PDAC development is a contentious issue. Long-term insulin use was not found to be a risk factor of PDAC development[173]. On the other hand, short-term insulin user (< 3-5 years) was found to have an elevated risk of PDAC (OR 5.60, 95%CI: 3.75-8.35)[173]. Perhaps this data reflects the other way around. It is likely that the worsening of hyperglycaemia or the severe hyperglycaemia requiring insulin injection might reflect the onset of PDAC or effect of PDAC on the

glycaemic control. Whereas few meta-analysis have suggested an elevated risk of PC in insulin users[174] the same evidence was not found in other studies[175] and also with newer insulin like glargine insulin[176]. In terms of survival benefit, insulin use had no impact on survival as shown in recent studies[120,177].

Insulin secretagogues like the sulfonylureas (SU) are also implicated as a risk modifier of PC. There are only few studies that have specifically looked into the link between SU and PC. However, studies including nation-wide cohorts[178], and meta-analyses[175] had pointed that SU use is associated an elevated risk of PC (OR varies between 1.5-1.7). However, with newer generation SU data is sparse and this association is further complicated by the effect of concurrent obesity and IR on the development of PC. Moreover, earlier analyses are met with significant methodological flaws and heterogeneity among studies[179].

Incretin based therapies: DPP-4 inhibitors and GLP-1 receptor agonist

Incretins are hormones secreted from the intestine and have a significant impact on the glycaemic control. GLP-1 analogues and inhibitors of dipeptidyl peptidase-4 (DPP-4) enzyme are established therapies for T2DM in clinical practice. Although there was a concern of acute pancreatitis and PC associated with their use from the initial preclinical[180] and adverse database review[181] studies, data regarding the risk for PC was inconsistent. Hence, both United States Food and Drug Administration and European Medicines Agency advised on continuous follow-up of patients started on these therapies for these two adverse events[182].

Earlier meta-analysis also did not find an increased risk of PC with DPP-4i treatment group[183]. Moreover, the recent meta-analysis involving 157 trials reporting PC (66897 patients in DPP-4 inhibitors and 61597 patients in control group) showed no associated risk with DPP-4 inhibitors use (OR: 0.84 [95%CI: 0.69-1.03], I^2 [for heterogeneity] = 0%). This association was found across different types of DPP-4i molecules and thus possibly reflects a class effect. Data from large population based studies also showed similar reassuring findings[184]. Due to several limitations of the trials like a shorter follow-up, reporting bias, small number of PC cases, it is important to keep a watch over this association in future. Moreover, one meta-analysis of the large cardiovascular outcome trials on DPP-4i showed an 75% increased risk of pancreatitis[185]. Such findings warrant longer duration follow-up studies and continued vigilance. A study[186] has shown that DPP-4i may be associated with increased risk of pancreatitis and PC in short-term without any relationship with exposure duration, thus implying that it might be the result of reverse causality rather than the DPP-4i exposure itself.

Similarly, more data are now available for different GLP-1 analogues. The larger cardiovascular outcome trials did not find any elevated risk of PC in GLP-1 analogue users[187,188]. Consequently, an updated pooled analyses from the cardiovascular outcome trials also did not show an excess risk of PC or pancreatitis with use of GLP-1 analogues[185]. However, it is noteworthy that such trials are not primarily meant to detect any increased malignancy risk. Thus, although the data is reassuring, a continued vigilance is warranted.

Other drugs (thiazolidinediones and sodium-glucose co-transporter type 2 inhibitors)

The other antidiabetic drugs are thiazolidinediones (TZD) and sodium-glucose co-transporter type 2 (SGLT-2) inhibitors. TZDs like pioglitazone and rosiglitazone primarily act through activation of the peroxisome proliferator-activated receptor-gamma pathway. This activation has direct and indirect implications in the PC biology. TZDs have shown to have inhibiting effect on several aspects of PC including cell proliferation and metastasis[189-191]. It also has the potential to modify the risk of PC through insulin sensitization, modification of the obesity and the inflammation [192]. However, these promising experimental findings of benefits of TZD have been replicated in clinical studies with mixed results.

While two meta-analyses did not find any association between TZD use and the risk of PC[175,193], one population based study had shown a protective role of TZDs against PC[178]. On the other hand, Lewis *et al*[194] demonstrated that TZD use might be associated with an increased risk of PC. As far as the prognostic role is considered, TZDs did not have any effect on survival[195,196].

SGLT2-inhibitors are the newest class of oral antidiabetic medication and have already made its place in the therapeutic algorithm of diabetes, owing to its cardiovascular benefits. Functional SGLT-2 are detectable in PC cells and hence, it was hypothesized that SGLT-2 inhibitors can inhibit tumour growth by blocking the entry

of the glucose within the cell[197]. An experimental study has shown canagliflozin, a SGLT-2 inhibitor to inhibit PC growth[198]. However, clinical studies are yet to confirm its effect on PDAC survival.

CONCLUSION

In this review, we have summarized the intricate relationship between DM and PC. Long-standing diabetes is considered as a risk factor for development of PC. On the other side, NOD in an elderly patient can be a manifestation of underlying PC. Though the exact mechanism remains to be eluded in future studies, the mechanism of the development of NOD in PC involves both IR and islet cell dysfunction. Diabetes has also been suggested to have an unfavourable effect on the overall survival of patients with PC.

Early detection of PC in a patient with DM is of utmost important and is a clinically challenging task. PC has a low prevalence in both general population and diabetes subjects. Thus, devising a strategy to screen diabetes population for PC is the need of the hour. There is an urgent need for a clinically useful and cost-effective screening tool to detect PC among patients with long-standing diabetes. The epiphenomenon of NOD can subserve as a potential clue along with recent onset worsening of glycaemic control and a continued weight loss. Apart from clinical pointers, many biomarkers have also been found to differentiate PC related DM from the commoner T2DM. Moreover, different clinical and biochemical parameters have been combined to develop different screening tools. Proper screening and early recognition of PC can improve the outcome of this devastating neoplasm.

Can we delay the occurrence or halt the progression of PC in a patient of DM? The strategies to improve IR like regular physical exercises, intermittent fasting, or low-fat diet can be explored in future. Moreover, other healthy behaviours like smoking cessation should be implemented in patients with long-standing DM. The role of glucose lowering medications like metformin in delaying the occurrence of PC needs to be explored further in longitudinal studies.

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