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RESEARCH ARTICLE

DIABETES MANAGEMENT AND PANCREATIC CANCER A NARRATIVE LITERATURE REVIEW

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Abstract

Diabetes mellitus and pancreatic ductal adenocarcinoma (PDAC) have a bidirectional relationship in which long-standing type 2 diabetes may contribute to cancer susceptibility, while occult pancreatic cancer may induce new-onset diabetes or worsen pre-existing glycemic control. This narrative review critically synthesizes 18 articles published between 2017 and 2026, including observational studies, systematic reviews, meta-analyses, and narrative reviews. The available evidence supports an association between diabetes and pancreatic cancer, although reverse causality, confounding, and differences in diabetes classification complicate causal interpretation. Recent-onset or rapidly worsening diabetes, particularly when accompanied by unexplained weight loss or pancreatic symptoms, may provide an opportunity for earlier cancer detection. However, existing prediction models require further validation, and diabetes alone does not justify universal pancreatic cancer screening. Proposed biological mechanisms include insulin resistance, hyperinsulinemia, chronic inflammation, and tumor-related endocrine dysfunction, particularly impaired β -cell function. Associations between glucose-lowering medications and pancreatic cancer incidence or survival remain influenced by treatment selection, comparator groups, and methodological biases. Metformin has not been established as an effective strategy for pancreatic cancer prevention or improved survival, while observed associations involving insulin do not demonstrate a causal carcinogenic effect.

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In patients with established PDAC, diabetes management should prioritize safe glycemic control, adequate nutrition, assessment of pancreatic exocrine insufficiency, and individualized treatment adjustments during cancer therapy and

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following pancreatic resection. Further prospective research is needed to validate targeted early-detection strategies and determine whether optimized metabolic management improves clinical outcomes.

Introduction:-

Diabetes mellitus comprises metabolic disorders characterized by persistent hyperglycemia arising from impaired insulin secretion, insulin action, or both. In conventional type 2 diabetes mellitus (T2DM), insulin resistance and progressive β -cell dysfunction interact. Pancreatic disease can also produce diabetes, creating a clinically important connection between endocrine and exocrine pancreatic function. In pancreatic ductal adenocarcinoma (PDAC), the predominant form of pancreatic cancer addressed in this literature, diabetes may precede the malignancy, emerge as a consequence of an occult tumor, or worsen during cancer treatment and pancreatic resection. These possibilities require different interpretations of the same observation: a patient with both diabetes and pancreatic cancer. [1, 2]

The relationship is bidirectional. Long-standing T2DM and its associated metabolic environment may contribute to susceptibility, whereas recent-onset or rapidly worsening diabetes may be a manifestation of PDAC. Weight loss accompanying deteriorating glycemia is especially relevant because it differs from the common metabolic context of newly diagnosed T2DM. Nevertheless, most people with diabetes do not develop pancreatic cancer, and neither diabetes nor weight loss alone establishes a cancer diagnosis. Distinguishing a risk factor from a marker of existing disease is essential when interpreting epidemiological findings and considering early detection. [3, 4] Diabetes management adds a further layer of complexity. Glucose-lowering drugs differ in their mechanisms, indications, and position in the course of diabetes. Associations between a medication and cancer may therefore reflect the drug, the underlying disease, treatment selection, or metabolic changes caused by an undiagnosed tumor. After cancer diagnosis, management must also account for impaired insulin secretion, nutritional decline, exocrine insufficiency, and treatment-related changes in glucose regulation. This review examines these relationships, separating evidence concerning cancer incidence, early detection, prognosis, and the practical management of diabetes in pancreatic disease. [1, 3]

Materials and Methods:-

A narrative literature review was conducted using a predefined corpus of 18 articles available as full-text PDFs. Publication years ranged from 2017 to 2026. The corpus comprised five observational clinical or population-based studies, five systematic reviews or meta-analyses, and eight narrative, symposium, or consortium reviews. All 18 articles contributed to the synthesis. The review was designed to critically integrate this corpus rather than to estimate all available evidence through a new systematic database search. Each article was examined for its study design, population, definition and timing of diabetes, medication exposure, comparison group, cancer outcome, adjustment strategy, and principal limitations. The synthesis was organized around diabetes classification, bidirectional disease mechanisms, early detection, glucose-lowering treatments, prognosis, and management after PDAC diagnosis. Primary observational findings were distinguished from studies described secondarily within reviews. No new meta-analysis, formal risk-of-bias scoring, or certainty-of-evidence grading was performed.

Bibliographic details, publication year, DOI, sample sizes, and numerical findings used in the manuscript were checked against the source PDFs, including the relevant tables and figures. Publication years were taken from the journal article rather than filenames or the year embedded in a DOI. Targeted publisher or bibliographic-index checks clarified incomplete publication details and an author-name ordering discrepancy in an accepted manuscript; they did not expand the clinical source corpus. Where source text and tables disagreed, the discrepancy was identified and the affected finding was omitted or described with its exact table-defined context. The analysis preserved the distinction between odds ratios (ORs), hazard ratios (HRs), and risk ratios (RRs); confidence intervals are 95% unless stated otherwise. Effect estimates were interpreted according to their original reference groups and exposure windows. Particular attention was given to reverse causality, confounding by indication, immortal-time bias, sparse cancer events, selection of patients already diagnosed with cancer, and variation in definitions of new-onset diabetes. A predefined corpus cannot establish completeness of literature coverage, and overlapping primary studies within reviews were not treated as independent replications.

Discussion:-

Diabetes classification and the significance of timing:-

Pancreatogenic diabetes, often termed type 3c diabetes, includes diabetes associated with disorders of the exocrine pancreas, such as chronic pancreatitis, PDAC, and pancreatic resection. It is not synonymous with either conventional T2DM or PDAC-associated diabetes alone. Chronic pancreatitis can impair insulin production through islet injury and loss, while cancer-associated diabetes may involve functional endocrine disturbances before extensive tissue destruction. The 2026 CPDPC review emphasizes that validated, universally accepted diagnostic

criteria remain lacking. Exocrine insufficiency, abnormal pancreatic imaging, and absence of type 1 diabetes autoimmunity are useful elements of proposed classification schemes, but do not constitute a prospectively validated diagnostic rule. [1, 5] Timing is equally important. The sources define new-onset diabetes differently: Amri et al. used onset within one year of, or concurrent with, cancer diagnosis; Li et al. used a duration of two years or less; other reviews discuss a three-year window. These categories should not be merged into a single uniform exposure. A first recorded diagnosis can also occur well after biochemical hyperglycemia begins. Analyses based on medical coding, glucose measurements, and patient-reported duration may therefore assign the same biological process to different categories. [3, 6, 7] Pre-existing T2DM does not exclude a subsequent tumor-related deterioration in glycemia. Conversely, not every recent diabetes diagnosis in a person later found to have PDAC is necessarily caused by the tumor. Classification should consider the trajectory of glucose control, weight, symptoms, pancreatic disease, and treatment rather than rely exclusively on a duration threshold. The evolving mechanistic literature also cautions against assuming that all PDAC-associated diabetes has the same balance of insulin resistance and secretory failure. [5, 8]

Association with cancer risk and the problem of reverse causality:-

The population-based study by Kim et al. provides evidence that pancreatitis modifies the diabetes–cancer association. In a Korean nationwide nested case-control analysis with 60,716 pancreatic cancer cases and 546,444 control observations, the main analysis applied a one-year lag. Relative to individuals with neither diabetes nor pancreatitis, the adjusted OR was 1.65 (1.61–1.68) for T2DM alone, 4.71 (4.12–5.37) for post-pancreatitis diabetes, and 4.96 (4.48–5.49) for T2DM followed by pancreatitis. These are comparisons with a common disease-free reference group, not estimates of the causal effect of changing diabetes treatment. [9] Shorter lag periods produced stronger associations in that study. This pattern is compatible with occult cancer causing metabolic deterioration or pancreatitis before the malignancy is diagnosed. Associations persisted with longer lag periods, which supports a longer-term relationship but does not fully eliminate residual confounding or undetected cancer. Importantly, an estimate highlighted in the abstract for post-pancreatitis diabetes, OR 8.83 (5.99–13.01), corresponds specifically to 730–1,094 days of diabetes duration in Table 4, an analysis without a lag period. It should not be generalized to every patient with diabetes of less than three years' duration. [9]

Genetic evidence offers a complementary perspective. Wu et al. pooled Mendelian randomization studies and reported an OR of 1.09 (1.04–1.15) for pancreatic cancer in relation to genetic liability to T2DM. Such evidence is less directly vulnerable to cancer causing a recent diabetes diagnosis. However, interpretation depends on valid genetic instruments and assumptions concerning pleiotropy and pathways linking the instruments to cancer; heterogeneity also limits generalization. Genetic liability represents lifelong susceptibility and does not measure the effect of a particular glucose-lowering drug, a lower HbA1c achieved in clinical care, or the reversal of established diabetes. The result supports a possible causal contribution of T2DM-related biology, rather than demonstrating that intensified glycemic treatment prevents PDAC. [10]

Clinical phenotype and the interpretation of cancer cohorts:-

Yoon et al. compared 127 patients classified as having PDAC-associated type 3c diabetes with 127 medical T2DM controls. The former were older, with median age 66 versus 61 years, lower median body mass index, 25.9 versus 32.1 kg/m², and lower median HbA1c, 7.0% versus 8.8%; each comparison had $P < .001$. Cancer-associated patients more often had symptoms such as jaundice, abdominal pain, reduced appetite, or weight loss. These observations demonstrate clinical differences within selected populations, but do not establish a validated screening rule. The cancer group came from a resected PDAC cohort and the controls from a medical diabetes population; the analysis included both new-onset and worsening diabetes and is vulnerable to referral and selection effects. A comparatively lower HbA1c should therefore not be interpreted as reassurance when other concerning features are present. [11]

Hospital cohorts describe the burden of coexisting diabetes among people who already have PDAC. Amri et al. reported diabetes in 75 of 197 patients (38.1%) at a Moroccan center. Li et al. reported 536 patients with diabetes among 1,620 patients with PDAC (33.1%); 287 had new-onset diabetes, 210 long-standing diabetes, and 39 unknown duration. These proportions are prevalence within cancer cohorts. They cannot estimate the probability of cancer in a general diabetes population or prove that diabetes caused the malignancy. The Amri article contains conflicting weight-loss frequencies in its text and tables, so an exact weight-loss percentage is not used here. [6, 7]

Biological mechanisms and their evidential limits:-

Several pathways make a long-term diabetes–PDAC association biologically plausible. Obesity and insulin resistance can produce hyperinsulinemia, altered adipokine signaling, and chronic inflammation. Insulin and insulin-like growth factor (IGF) signaling may influence pancreatic epithelial cells, stellate cells, and the stromal environment. Eibl et al. describe interactions among islets, inflammatory cells, fibrosis, and neoplastic tissue, while

Andersen et al. discuss the local exposure of exocrine pancreatic tissue to islet-derived insulin. These mechanisms draw on experimental models and human observations, but do not identify the magnitude of a preventable drug-mediated cancer risk in an individual patient. [1, 2] Włodarczyk et al. review the IGF axis as a potential link between metabolic disease and PDAC and as a candidate source of early-detection biomarkers. Biological involvement does not establish adequate sensitivity, specificity, or clinical benefit for an IGF-based diagnostic test. Similarly, proposed tumor-derived mediators, including adrenomedullin-containing extracellular vesicles, can impair β -cell function in experimental systems. Hill et al. distinguish PDAC observations from hypotheses extrapolated from islet physiology, particularly those concerning α - and δ -cell regulation, microvascular exchange, and extracellular matrix remodeling. These remain promising research directions rather than established clinical assays or therapeutic targets. [8, 12]

More recent physiological evidence also refines older explanations centered on insulin resistance. The CPDPC review reports interim DETECT observations in which recent PDAC-associated diabetes showed greater insulin sensitivity and more impaired β -cell function than conventional T2DM, with inappropriate meal-related glucagon responses. This does not mean that insulin resistance is absent in all PDAC, but it supports a prominent role for defective insulin secretion and endocrine dysregulation in some patients. Mechanical destruction of the gland alone is consequently an incomplete model, and metabolic phenotypes may vary with disease stage, pre-existing T2DM, nutritional state, and treatment. [5, 8]

Early detection through changes in diabetes:-

Recent-onset diabetes, rapid deterioration in previously stable diabetes, and weight loss accompanying increasing glucose provide a rationale for risk assessment. Sharma and Chari describe strategies that combine age, changes in weight, and changes in glucose, including the END-PAC framework. The surgical review by Khadka et al. likewise emphasizes the potential diagnostic opportunity presented by new metabolic changes. These sources support clinical vigilance and investigation of concerning presentations, but the recognition of an association does not itself demonstrate that screening all patients with diabetes improves survival. [3, 13]

Cong et al. reviewed 18 studies addressing risk factors or prediction and evaluated 13 prediction models. Their pooled c-index was 0.79 (0.75–0.84) in training datasets and 0.79 (0.71–0.87) in validation datasets, with substantial heterogeneity. Discrimination describes a model's ability to rank risk; it does not establish calibration, positive predictive value, an acceptable number of false-positive investigations, or a reduction in cancer mortality. Sparse positive cases, inconsistent follow-up, incomplete reporting of sensitivity and specificity, and limited stage-specific information constrain clinical interpretation. Apparent predictors such as weight loss or medication escalation may be consequences of an existing tumor rather than causes of future disease. [14]

The corpus therefore supports prospective evaluation of targeted approaches rather than a universal imaging policy based on diabetes alone. Such studies should measure detection of resectable disease, false-positive procedures, harms, resource use, and patient outcomes. CA19-9 and experimental molecular or hormonal markers cannot be assumed to distinguish PDAC-associated diabetes reliably from T2DM. CA19-9 interpretation is also complicated by cholestasis and metabolic abnormalities in cancer cohorts. Clinical symptoms requiring diagnostic assessment should be distinguished from screening an otherwise asymptomatic population. [3, 7, 12, 14]

Glucose-lowering drugs and pancreatic cancer incidence:-

Medication studies must be interpreted within the natural history of diabetes. Metformin often appears earlier in treatment, whereas insulin commonly marks more advanced secretory failure, difficult glycemic control, or pancreatic disease. An occult tumor can worsen glucose control and trigger insulin initiation shortly before cancer diagnosis, producing protopathic bias: treatment is associated with the illness because it responds to an early manifestation of that illness. Confounding by indication, differences in diabetes duration and severity, and greater diagnostic attention after treatment initiation can all imitate a drug effect. [3, 15] Szymczak-Pajor et al. pooled 16 observational publications and reported a modest association between metformin and lower pancreatic cancer incidence compared with other antidiabetic drugs, RR 0.94 (0.91–0.98). The direction varied by comparator: reported RRs were 0.73 (0.69–0.77) versus sulfonylureas and 0.60 (0.53–0.68) versus insulin, but 1.16 (1.02–1.32) versus thiazolidinediones and 1.45 (1.33–1.59) versus DPP-4 inhibitors. This comparator dependence argues against describing metformin as uniformly superior for cancer prevention. The review used a fixed-effect approach despite marked heterogeneity and lacked consistent information on HbA1c, diabetes duration, obesity, or treatment exposure. Some forest-plot rows repeat a study's metformin cohort across different comparator groups, so the pooled participant totals should not be interpreted as counts of unique individuals. The estimates remain observational associations. [16]

Chen et al. followed 3,118,538 adults in British Columbia and identified 7,540 pancreatic cancer cases. Their time-varying analyses incorporated a one-year lag and found positive associations for insulin exposure and some insulin secretagogues. However, the primary reference groups included people without diabetes, leaving important differences in underlying disease and treatment need. A smaller active-comparator analysis among new users, with pioglitazone as the reference, yielded HRs of 0.33 (0.08–1.31) for metformin and 1.49 (0.33–6.63) for basal insulin. The wide intervals include no association and illustrate the limited precision of the more clinically comparable analysis. The study does not establish either metformin protection or insulin-induced cancer. [15]

The insulin-stratified findings of Kim et al. require similar care. Continuous insulin users with post-pancreatitis diabetes had an adjusted OR of 16.72 (9.50–29.43), based on 34 cases and 19 control observations in that subgroup. The reference was individuals with neither diabetes nor pancreatitis, not otherwise comparable patients with post-pancreatitis diabetes who did not receive insulin. Severe pancreatic endocrine dysfunction or undiagnosed cancer could explain part of the association. This result may identify a group warranting further study, but cannot justify withholding insulin when it is needed. [9]

Randomized evidence should help separate treatment effects from these biases, but pancreatic cancer is uncommon and often not a prespecified outcome in diabetes trials. An et al. assembled a network meta-analysis; its pancreatic cancer network included 31 studies, 165,210 participants, and 176 events. A material reporting problem prevents straightforward interpretation: the pancreatic cancer results label a negative value, -1.27 , as an OR, with an interval of -3.30 to 0.75 , while asserting a significant reduction. An OR cannot be negative; if these values were intended to represent log-odds ratios, the interval would cross the null value of zero. The scale cannot be repaired by assumption. Accordingly, the reported drug ranking is not used here as evidence of a preventive effect. The article itself also recognizes that sparse events and SUCRA rankings do not establish clinical superiority. [17]

For incretin-based therapies and SGLT2 inhibitors, this corpus does not resolve long-term comparative pancreatic cancer effects. In the Chen cohort, the GLP-1 receptor agonist ever-use estimate was HR 0.73 (0.33–1.63), with only 18 cancer events; this is imprecise evidence, not proof of protection or definitive long-term safety. Reviews discuss laboratory mechanisms and differing observational signals, but cell-model antitumor effects should not be translated into a clinical indication. Drug selection should therefore follow the patient's metabolic needs and established treatment considerations rather than a cancer-prevention hierarchy derived from these papers. [4, 15, 16, 17]

Diabetes status, metformin, and survival after cancer diagnosis:-

Cancer incidence and survival after PDAC diagnosis are separate outcomes. Li et al. reported median overall survival of 9.15 months in new-onset diabetes, 11.64 months in long-standing diabetes, and 10.90 months without diabetes. However, the adjusted association of diabetes status with survival in the full cohort did not meet the conventional significance threshold ($P = .054$); the authors reported an association in the curative-resection subgroup ($P = .039$). The published Cox table does not provide separate HRs for each diabetes-category contrast, preventing reconstruction of those effects. Stage, resection eligibility, jaundice, nutritional condition, and treatment may influence both the diabetes classification and survival. These findings do not demonstrate that improving glucose control would lengthen survival. [7]

The metformin survival meta-analysis by Xin et al. included eight retrospective cohorts comprising 4,293 patients with pancreatic cancer and diabetes. The random-effects pooled mortality HR was 0.81 (0.70–0.93). After exclusion of studies considered susceptible to immortal-time bias, the estimate was 0.86 (0.69–1.07), no longer statistically significant. Immortal-time bias can arise when patients must survive after cancer diagnosis long enough to receive the medication and are then classified as exposed. Better baseline health, earlier disease, or eligibility to continue oral medication may also favor metformin users. The sensitivity result materially weakens a causal survival claim. [18] Sharma and Chari further summarize randomized trials in advanced pancreatic cancer that did not demonstrate benefit from adding metformin to cancer treatment. These trials are secondary evidence within the supplied review, rather than independently examined trial reports in this corpus. Experimental effects on AMPK, mTOR, insulin signaling, or tumor metabolism offer hypotheses for further study, but do not establish metformin as an anticancer treatment. Its role in managing suitable patients with diabetes should be distinguished from any unproven indication to improve PDAC survival. [3, 4, 16]

Management when pancreatic cancer is established:-

The immediate purpose of diabetes care in PDAC is to manage hyperglycemia safely while supporting nutrition and cancer treatment. Assessment should consider pre-existing T2DM, tumor-associated endocrine dysfunction, pancreatic resection, changes in food intake, exocrine insufficiency, and treatment-related hyperglycemia. These

processes can coexist, so a single diagnostic label may not explain the patient's current insulin requirement. Insulin is often needed when secretory capacity is substantially impaired, especially after extensive pancreatic resection. The observational cancer associations described above provide no basis for replacing an otherwise necessary treatment. [1, 5, 8]

Management of exocrine and endocrine dysfunction should be coordinated. Pancreatic enzyme replacement is relevant when exocrine insufficiency causes maldigestion or malabsorption, alongside attention to nutritional status and fat-soluble vitamin deficiencies. Reviews describe potential improvements in incretin responses and nutrient-related insulin secretion after enzyme replacement, but this should not be presented as a proven cancer-modifying intervention. The 2026 CPDPC review identifies the need to validate these metabolic effects further. In established PDAC with involuntary weight loss, maintaining adequate nutrition has a different purpose from weight reduction strategies discussed for obesity-associated long-term risk. [1, 2, 5]

Hypoglycemia deserves particular attention in insulin-deficient pancreatic diabetes, especially where counter-regulatory dysfunction, malabsorption, or variable intake is present. Glucose monitoring and treatment adjustment must accommodate these changing circumstances. Metformin can be considered where concomitant insulin resistance and clinical suitability support its use, but the corpus does not establish an optimal glucose-lowering regimen or a PDAC-specific HbA1c target. Current management is largely extrapolated from other diabetes populations. Controlled studies of pancreatic diabetes are needed to evaluate glycemic benefit, hypoglycemia, tolerability, nutrition, and quality of life. [1, 5]

Resection also requires reassessment rather than an assumption that diabetes will resolve. Removal of tumor-related signals may improve glucose regulation in some patients, while loss of pancreatic tissue can create or aggravate insulin deficiency. Yoon et al. documented persistent postoperative glycemic abnormalities in their surgical cohort, and the surgical review by Khadka et al. emphasizes the need for postoperative endocrine and exocrine follow-up. Joint care across endocrinology, oncology, pancreatic surgery, and nutrition is therefore a practical implication of the bidirectional relationship. [5, 11, 13]

Limitations and priorities for research:-

The main limitation of this review is its predefined source corpus, which cannot support claims of exhaustive literature retrieval. Many included articles are reviews, and their primary studies can overlap. Observational studies differ in diabetes definitions, cancer ascertainment, treatment exposure, lag periods, and clinical settings; resected cohorts and hospital case series cannot be generalized directly to asymptomatic diabetes populations. Large sample sizes do not eliminate residual confounding, and statistically significant relative effects do not quantify an individual patient's absolute risk.

Source inconsistencies also affect interpretation. The negative values labelled as ORs in the network meta-analysis, conflicting weight-loss frequencies in a hospital cohort, and the difference between an abstract's duration summary and its underlying table show why exact estimates require verification. These findings were not silently corrected. More broadly, prediction accuracy, genetic susceptibility, observational medication associations, and experimental mechanisms answer different questions and should not be combined into a single claim of cancer prevention. [6, 9, 10, 14, 17]

Priorities are standardized definitions of PDAC-associated and post-pancreatitis diabetes; prospective validation of risk models in diverse diabetes populations; sufficiently long, carefully ascertained cancer outcomes in treatment studies; and active-comparator analyses that account for diabetes duration, HbA1c, severity, and treatment changes. Trials focused on pancreatic diabetes should evaluate safe glucose control and nutritional outcomes, while cancer-treatment trials should separately test any proposed antitumor benefit. No included evidence directly demonstrates that intensive glucose lowering prevents PDAC or that a specific glycemic target improves PDAC survival. [5, 14, 15, 16]

Conclusion:-

Diabetes and pancreatic cancer are linked through a combination of long-term metabolic susceptibility and tumor-related endocrine dysfunction. Recent-onset or rapidly worsening diabetes, particularly with unexplained weight loss or pancreatic symptoms, can provide a diagnostic opportunity, but diabetes alone does not establish a screening indication or a cancer diagnosis. Genetic and mechanistic findings support biological plausibility while leaving substantial uncertainty about preventable treatment effects. Medication studies suggest associations that depend strongly on comparator selection, disease severity, and bias. Metformin has not been established as superior for

PDAC prevention or as a survival-enhancing cancer treatment; observed insulin associations do not prove that insulin causes pancreatic cancer. Once PDAC is present, diabetes care should prioritize safe glucose management, adequate nutrition, exocrine assessment, and reassessment during treatment and after surgery. The central research need is prospective evidence that translates risk recognition and metabolic management into meaningful patient outcomes.

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