Pancreatic cancer and diabetes - a two-way street?

An integrative treatment using natural products and nutritional intervention

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Abstract

Pancreatic adenocarcinoma is one of the most lethal diseases with poor prognosis. Despite the advances achieved by radio-chemotherapy or targeted therapy over recent decades, the treatment has shown only little survival improvements. There is a strong aetiological correlation between diabetes-related mechanisms and the pathogenesis of pancreatic adenocarcinoma. The therapeutics from natural sources and nutritional intervention can represent the new option for how to address these mechanisms.

Several clinical studies suggested that constituents from *Curcuma longa*, *Nigella sativa*, *Glycine max* and *Ginkgo biloba* and a low-carbohydrate ketogenic diet combined with anticancer or antidiabetic drugs have the potential for the treatment of pancreatic adenocarcinoma or diabetes mellitus. They may address different disease-related pathways, attenuate drugs-resistance, reduce toxicity and adverse effects. However, the optimal therapeutic window or plants-drug interactions are yet to be considered.

Introduction to pancreatic cancer and diabetes mellitus

- Pancreatic ductal adenocarcinoma (PDAC) >90% of pancreatic malignancies
- PDAC maintains **poor prognosis** → incidence ≈ mortality

Cases	Deaths	Survival	Worldwide rates	
UK/worldwide ~10,000/338,000	UK/worldwide >9,000/330,000	<5% for 5 or more years	Rank	Country
			1	Hungary
			2	Uruguay
			3	Moldova
			4	Latvia
			5	Japan
			6	Slovakia
			7	Estonia
			8	Czech Republic

- Metastatic 80% of cases => average survival time 3-6 months [1-2]
- **Pancreatic cancer risk** – pancreatitis associated with prolonged inflammation, due to: toxic exposure (alcohol, smoking), vascular and acinar cell injury, infections, duct obstruction (e.g. biliary calculi), obesity, metabolic syndrome, diabetes mellitus (DM) [3]
- PDAC progression – precursor lesions / pancreatic intraepithelial neoplasia (PanIN) [10]

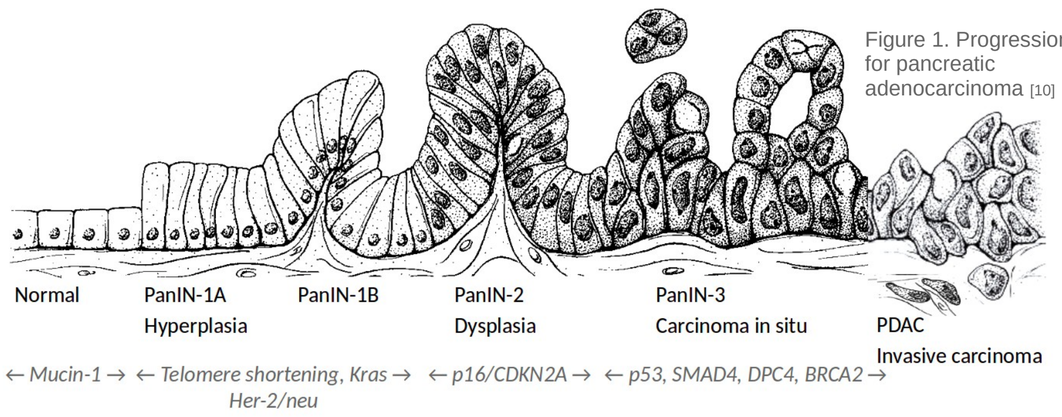


Figure 1. Progression for pancreatic adenocarcinoma [10]

- **Long-term type 2 diabetes** => 2-fold ↑ risk of PDAC

85% of cases with PDAC have impaired glucose tolerance or DM

- **Type 3c diabetes** (the new-onset/PDAC-associated DM) - precedes cancer by 2-3 years
- DM + chronic pancreatitis => ~up to 8-fold ↑ risk of PDAC
- PDAC and DM – **positive aetiologic correlation** [22-23]

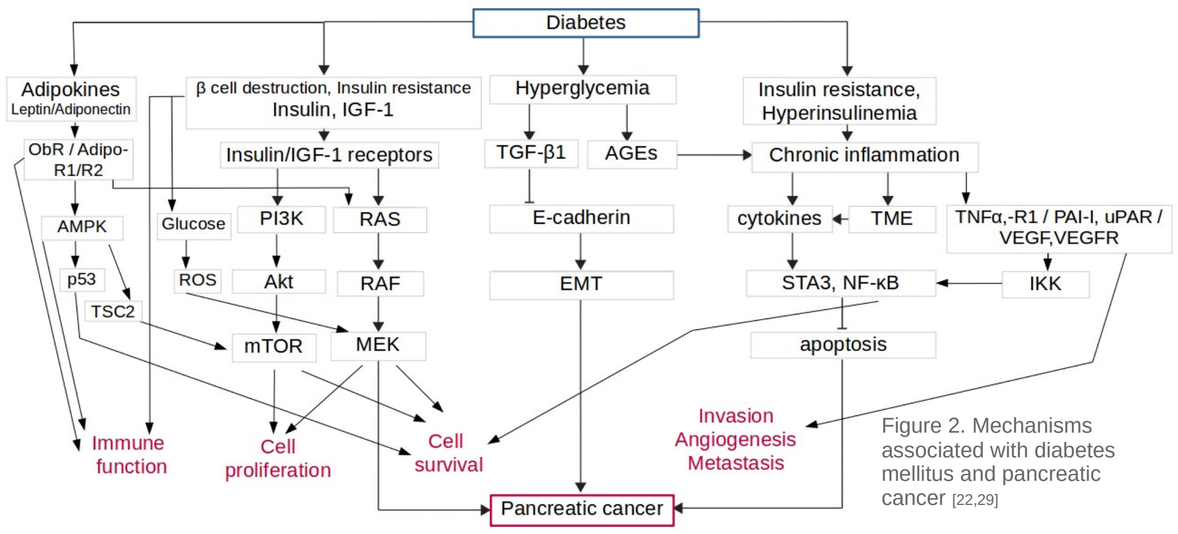


Figure 2. Mechanisms associated with diabetes mellitus and pancreatic cancer [22,29]

Risk and Opportunities

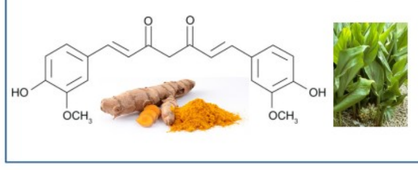
- Late diagnoses, radical resection, chemoradiotherapy, toxicity risks...
- 'Window of opportunity' for **integrative treatment strategies** → for the prevention and treatment of DM and PDAC pathological mechanisms
- **Natural products (NPs)** and **Low-carbohydrate ketogenic diet (LCKD)**
- "*A two-way street*" relationship: - DM and PDAC
  - allopathic medicine and complementary approaches

Methods

- A systematic review of 28 clinical studies using LCKD and NPs: Curcumin / *Curcuma longa* L., Thymoquinone / *Nigella sativa* L., Genistein / *Glycine max* (L.), *Ginkgo biloba* L.
- Indicated in both PDAC and T2D. Used as a monotherapy or in combination with chemo-/radio-therapy or current antidiabetic medication

Summary findings

Curcumin / *Curcuma longa* L.

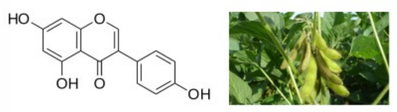


- +/- Gemcitabine / S-1
- NF-kB ↓, IL-6, IL-8, IL-10 ↓, COX-2 ↓, PSTAT3 ↓, CA19-9 ↓, hs-CRP ↓, fasting blood glucose ↓, fasting insulin ↓ ↑, HbA1C ↓, LDL ↓ HDL ↑, triglycerides ↓, Adiponectin ↑, HOMA-IR ↓ ↑, HOMA-β ↑, BMI ↓, ALT, AST ↓ [55-58,63-66]

Thymoquinone / *Nigella sativa* L.

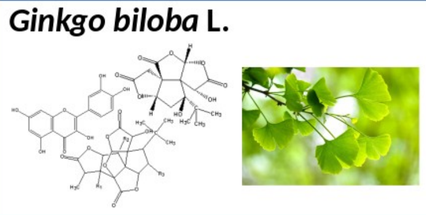
- CA19-9 ↓, overall improvement of cancer patients ↑, TNFα ↓, SOD, CAD, Gluthattione - antioxidants ↑, TBARS - lipid peroxidation ↓, MDA, NO pro-oxidants ↓, IL-1β ↓, fasting blood glucose ↓, HbA1c ↓, total cholesterol ↓, LDL ↓, triglycerides ↓, HDL ↑, AST ↓, ALT ↓, BMI ↓, insulin resistance ↓, β-cell function ↑ [59,67-69]

Genistein / *Glycine max* (L.)



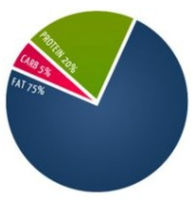
- + Gemcitabine, + Gemcitabine+Erlotinib
- CA19-9 ↓, fasting blood glucose ↓, HbA1c ↓, total cholesterol ↓, LDL ↓, triglycerides ↓, HDL ↑, VLDL ↓, fasting insulin ↓, HOMA-IR ↓, AST ↓ ALT ↓ [60-61,70-71]

***Ginkgo biloba* L.**

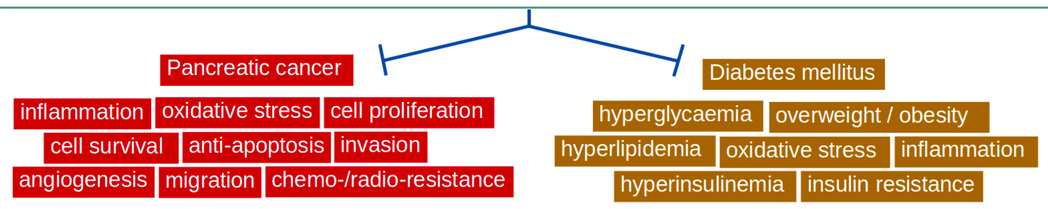


- + 5-fluorouracil, +/- metformin
- constant quality of life for cancer patients, fasting blood glucose ↓, HbA1c ↓, fasting insulin ↓, Insulin resistance ↓, BMI ↓, Visceral adiposity index ↓, AST ↑, ALT ↓, ALP ↓, lipid profile ø, urea ↓ creatinine ↓, RBC ↑, Hb ↑, Hct ↑ [62, 72-73]

Ketogenic diet



- +/- Gemcitabine/5-FU, Radiotherapy, or +/- calorie supplementation
- fasting blood glucose ↓, fasting insulin ↓, HbA1c ↓, B-hydroxybutyrate ↑, glucose ketone index ↓, HOMA-IR ↓, hs-CRP ↓, total cholesterol ↓, LDL ↓ ↑, HDL ↑ ↓, triglycerides ↓, VLDL ↓, BMI ↓, ALT ↓, AST ↓, ALP ↓, blood pressure ↓, T2D medication use ↓, inflammatory markers (IL-6,-8,-10, TNFα, MCP-1, I/V-CAM-1) ↓, VEGF ↓, WBC count ↑, Immune cells profile ↓ ↑ [74-82]



Conclusion and Recommendations

- PDAC - the most lethal disease, caused by multiple mechanisms
- Radio-chemotherapy is challenged by drug-resistance => Palliative management
- Areas for further research:

− to determine the **optimal therapeutic window** for NPs intervention

− to implement the **integrative approach** and to optimise the synergistic activity of **combined therapeutics**: poly-pharmaceutical preparations (chemo-radiotherapy or targeted therapy), poly-NPs formula, nutritional intervention

− to design the **therapeutic protocols and practices** on using evidence-based NPs and LCKD within integrative cancer treatment

− to introduce the **screening and early prevention programme:**

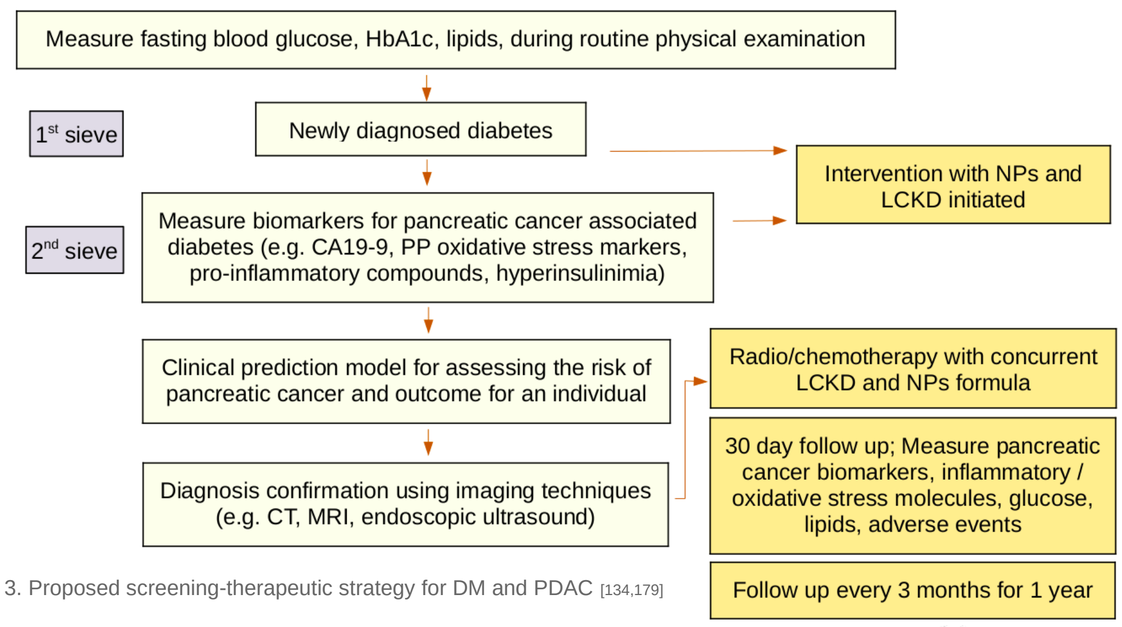


Figure 3. Proposed screening-therapeutic strategy for DM and PDAC [134,179]

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