Influence of antidiabetic drugs on glucose metabolism and immune response in patients with metastatic pancreatic ductal adenocarcinoma receiving gemcitabine plus nab-paclitaxel as first-line treatment

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a b s t r a c t

Background: Association between pancreatic ductal adenocarcinoma (PDAC) and type 2 diabetes mellitus (DM2) has long been evaluated. Indeed, DM2 can be both an epiphenomenon of PDAC and a risk factor. The present study aimed to investigate the correlation between overall survival (OS) and antidiabetic drugs in patients with metastatic pancreatic ductal adenocarcinoma and DM2.

Method: Data from 232 patients were collected retrospectively from 2014 to 2021. 174 from AOU Cagliari Medical Oncology and 58 from AOU Ancona Medical Oncology. All patients received gemcitabine plus nab-paclitaxel first-line chemotherapy. We aimed to evaluate the correlation between DM2, anti-diabetic medications and overall survival. Survival distribution was assessed by Kaplan-Meier curves.

Results: Median age was 68±9, 127 (55%) were male. 138/232 (59%) patients were not affected by DM2, 94/232 (41%) were affected by DM2. 57 were insulin-treated and 37 were metformin-treated. DM2 treated patients showed an higher median overall survival (26 vs 12 months, *p = 0,0002*). Among DM2 patients insulin-treated and metformin-treated showed an mOS of 21 months and 33 months, respectively.

Conclusions: Results showed a correlation between treated DM2 and higher mOS in patients with mPDAC. Limitations due to retrospective data collection must be considered. Further studies in this setting are needed.

1. Introduction

Pancreatic cancer (PC) is a highly malignant digestive tract tumor with a poor prognosis. It is the seventh leading cause of cancer death worldwide, but it will become the second in the next decade. The term 'pancreatic cancer' usually refers to ductal adenocarcinoma (PDAC), which accounts for 85% of all PCs. Unlike many other cancer entities, 5-year overall survival has improved marginally in recent decades but still does not exceed 9% [1,2]. Pancreatitis, obesity, smoking, alcohol consumption, and type 2 diabetes are risk factors for sporadic PDAC [3,4].

Diabetes mellitus is defined by the American Diabetic Association (ADA) as a group of metabolic diseases characterized by chronic hyperglycemia resulting from impaired metabolism of carbohydrates, fats, and proteins. Type 1 diabetes (DM1), also known as insulin-dependent diabetes mellitus (IDDM), results from the autoimmune destruction of pancreatic beta-cells. Type 2 diabetes mellitus (DM2), also known as non-insulin-dependent diabetes mellitus (NIDDM), is caused by insulin resistance (IR) and a relative deficiency of insulin secretion. Recently described, type 3c diabetes, also known as pancreatogenic diabetes, results from pancreatic diseases involving the exocrine and digestive functions of the pancreas. Chronic pancreatitis and PC are often the cause, and it responds differently to antidiabetic medications (ADMs) than type 1 or 2 diabetes [5].

DM2 is the most common type, accounting for about 90–95% of cases [6]. It is also assciated with a higher body mass index (BMI),

making it an independent risk factor for PDAC. Obesity and DM2 act synergistically to induce PC development. Obese patients have a higher degree of IR, making them prone to DM2. Several studies have shown that about 85% of patients had concomitant diabetes at the time of PC diagnosis [7–9]. In fact, it is associated with a 4-fold increased risk of PDAC [9–11]. The metabolic disorders associated with DM2, such as hyperinsulinemia, hyperglycemia, chronic inflammation, and abnormalities in insulin/insulin-like growth factor 1 (IGF-1) pathways, are involved in the PDAC development and may contribute to worse cancer morbidity and mortality [12–17].

DM2 represents not only a risk factor but also an epiphenomenon of PDAC. New-onset diabetes is present in 15%−35% of patients with PDAC [9,18–20]. As mentioned above, this is the so-called type 3c diabetes, which can be an early sign of PC.

Current medical treatments for DM2 include insulin or insulin analogs, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 agonists (GLP-1), and dipeptidyl peptidase IV inhibitors (DPP-4), drugs that reverse IR such as biguanides, and other drugs such as α-glucosidase inhibitors.

Metformin (1,1-dimethyl biguanide hydrochloride) is the only available biguanide. It has been the most widely used oral hypoglycemic agent in the treatment of DM2 since the 1950s. According to the most important diabetes associations, it is the recommended first-line glucose-lowering drug for people with DM2 [21,22]. Metformin acts as a glucose-lowering agent reducing hepatic gluconeogenesis and increasing peripheral glucose uptake in target tissues (such as skeletal muscles and fatty tissue). Additionally, it also reduces insulin levels by improving insulin sensitivity [23]. Several studies indicated that metformin could decrease the PC risk, activating the liver kinase B1 (LKB1)-adenosine monophosphate protein-activated kinase (AMPK) pathway and inhibiting hepatic gluconeogenesis and cancer cell proliferation. The LKB1-AMPK pathway is a potent mTOR inhibitor, regulating cellular proliferation and growth [17]. Metformin also disrupts NF-κB and hypoxia-inducible factor 1-alpha (HIF-1α), inhibiting vascular endothelial growth factor (VEGF) and inflammatory cytokines such as IL-1, IL-6, and TNF-α [24,25].

Insulin therapy is often necessary for longstanding DM2. Several epidemiological studies showed that insulin therapy is associated with an increased PDAC risk, as insulin can directly increase cancer risk. In vitro, higher insulin levels promote PC cell proliferation and glucose uptake by activating MAPK and PI3K pathways and increasing IGF-1 expression. Activation of the IGF-1 pathway by insulin has potential mitogenic and anti-apoptotic effects on cultured cancer cells [26–32]. The potentially alarming increase in cancer risk in insulin-treated patients suggested by many epidemiological studies, supported by the results of in vitro investigations, has not been confirmed by randomized clinical trials [33–39].

Furthermore, the data on the influence of DM2 and concomitant drug therapy in the progression of pancreatic neoplasms are conflicting. Some data suggest an antitumor effect of metformin in patients with different cancer types [40,41]. However, this clinical impact must be confirmed in the long-term follow-up. Preclinical evidence shows that insulin and IGF-1 promote cancer growth [42]. However, further retrospective analyses have been inconsistent. There is no solid clinical evidence that exogenous insulin is independently associated with worse outcomes in PC [43–45].

Understanding the real association between DM2, metformin, insulin use, and survival in PC could help guide clinical decision-making and prioritize potential therapeutic targets in this deadly disease.

Therefore, the present study investigated the correlation between clinical outcomes and antidiabetic drugs in patients with metastatic PDAC and DM2.

2. Materials and method

Data from 232 patients were collected retrospectively from 2014 to 2021. 174 from the Department of Medical Oncology of the University Hospital of Cagliari and 58 from the Department of Medical Oncology, AOU Ospedali Riuniti di Ancona. All patients were affected by metastatic pancreatic ductal adenocarcinoma and received gemcitabine plus nab-paclitaxel first-line chemotherapy. Patients with type 2 diabetes mellitus included in the study had been diagnosed with diabetes at least 12 months prior to the diagnosis of PDAC and had been treated with insulin or metformin. This time lapse between of diabetes and pancreatic cancer diagnoses was aimed to exclude from evaluation patients with new onset type 3c diabetes which is specifically linked to chronic pancreatic diseases and pancreatic cancer, and it has a different response to ADMs than type 1 or 2 diabetes.

Only patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤1 were included in the study. These patients showed no other relevant comorbidities. The primary objective of this study was to evaluate the association between insulin and metformin treated type 2 diabetes mellitus and overall survival in PDAC patients. The primary endpoint was OS. The secondary objectives were progression free survival (PFS) and to evaluate the influence of variables such as sex, ECOG PS, number of metastatic sites, Ca19.9 values, neutrophil to lymphocyte ratio (N/L ratio), and lactate dehydrogenase (LDH) values on OS and clinical outcome in patients with DM2.

Statistical analysis was performed with MedCalc Statistical Software version 14.10.2. Survival probability over time was estimated by the Kaplan-Meier method. Significant differences in survival probability between the strata were evaluated by log-rank test. For statistical analysis, OS was evaluated at endpoint, defined as the interval between the date of beginning of chemotherapy and death or last follow-up visit for patients who were lost to follow up. Cutoff values for Ca19.9 serum values, N/L ratio, and LDH serum values were calculated with the receiver operating characteristic (ROC) curves. We performed multivariate analysis for all survival variables (sex, ECOG PS, number of metastatic sites, Ca19.9 values, N/L ratio, and LDH values).

This study was performed in accordance with the study protocol, the ethical principles stated in the Declaration of Helsinki, as well as those indicated in the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP; ICH E6, 1995), and all applicable regulatory requirements.

3. Results

The median age was 68±9, 127/232 (55%) were male, 105/232 (45%) were female. 123/232 (53%) patients had an ECOG-PS 0, and 109/232 (47%) patients had an ECOG-PS 1. All patients received first-line treatment with gemcitabine plus nab-paclitaxel. 94/232 (41%) were affected by type 2 diabetes mellitus and 138/232 (59%) were not. Among DM2 patients, 57/94 were insulin-treated and 37/94 were metformin-treated (Table 1).

Among non DM2 patients, 87/138 had and ECOG-PS 0 and 51/138 had an ECOG-PS 1. In DM2 insulin-treated patients 41/57 had an ECOG-PS 0 and 16/57 had an ECOG-PS 1. In DM2 metformin-treated patients 28/37 had an ECOG-PS 0 and 9/37 had an ECOG-PS 1. DM2 patients showed a statistically significant higher median overall survival than no DM2 patients: 26 months (95% CI 15.00–33.00) versus 12 months (95% CI 9.00–14.00), respectively *(p = 0,0002)* (Fig. 1).

Within the DM2 group, median overall survival of metformin-treated patients was higher than insulin-treated and no DM2 patients: 33 months (95% CI 33.00–3.00) versus 21 months (95% CI
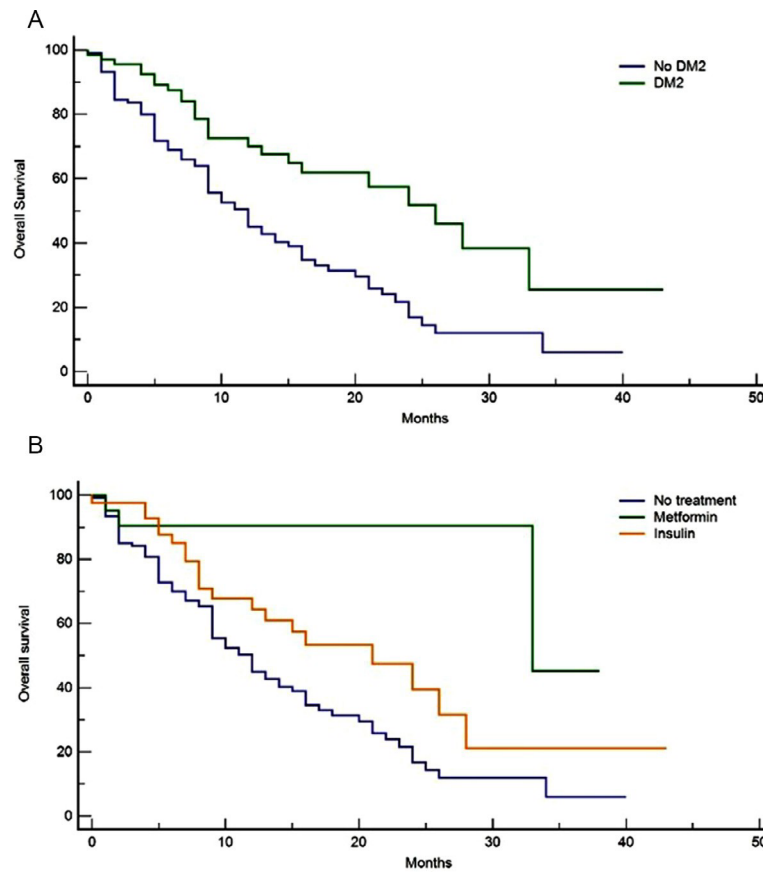
Fig. 1. A. Overall survival no type 2 DM and treated type 2 DM; B. Overall survival in no DM2 and DM2 (insulin and metformin treated patients).

Table 1
Patients characteristics.

Patients characteristics			tot
Median age			68±9
M/F			127/105

	No DM	*Insulin*	*Metformin*	
Number	138	57	37	232
ECOG-PS 0	87	51	28	166
ECOG-PS 1	51	16	9	76
1st line GEM-ABX	138	57	37	232
2nd line 5FU-based	137	57	34	228

12.00–28.00) versus 12 months (95% CI 9.00–14.00), respectively (*p* = 0,0002).

DM2 patients showed a statistically significant higher median progression free survival than no DM2 patients: 9 months (95% CI 6.00–11.00) versus 7 months (95% CI 6.00–8.00), respectively *(p = 0,02).*

Within the DM2 group, median progression free survival of metformin-treated patients was higher than insulin-treated and no DM2 patients: 11 months (95% CI 6.00–31.00) versus 8 months (95% CI 6.00–9.00) versus 7 months (95% CI 6.00–8.00), respectively, although this difference is not statistically significant *(p = 0,10)* (Fig. 2).

Finally, we performed multivariate analysis including sex, DM2, Ca19,9 values, N/L ratio, LDH values, number of metastatic sites and ECOG, that showed treated-DM2 is an independent prognostic factor *(p = 0.03).*

4. Discussion

Cellular metabolism represents one of the key factors for interpreting the results. The mechanisms to be considered are numerous and interconnected on several levels. In normal cells, the energy necessary for cellular processes is obtained through oxidative phosphorylation in the mitochondria. While, in cancer cells, to sustain rapid growth and proliferation, a large part of the glucose metabolism is shifted from oxidative phosphorylation to anaerobic glycolysis (effect Warburg) [46]. Although apparently disadvantageous, this "metabolic reprogramming" allows cell proliferation in tissue with fluctuating oxygen concentrations. Furthermore, metabolic intermediates of the process, such as lactate and glutamine, exert functions of support for tumor growth, maintaining TME oxidized, and contributing to cancer infiltration and immune evasion [47]. Carcinogenic mutations drive this metabolic shift in PI3K-AKT-PTEN pathway, and, in turn, these mutations are induced according to feedback from changes in metabolic cofactors and enzymes [48,49].

Notably, PDAC has a marked metabolic phenotype, and the expression of the glycolysis genes would seem to be regulated by the mutated KRAS [50]. This pathway plays a crucial role in regulating the transcription of glycolysis genes and glucose transporters [51]. Moreover, PDAC showed increased pyruvate carboxylation and glucose oxidation via the pyruvate dehydrogenase pathway in vivo [52]. Several studies have proposed metabolic classifications of PDAC [53,54], among them Karasinska et al. [55], through the evaluation of gene expression alterations in the glycolysis pathway and cholesterol synthesis, have identified 4 metabolic subgroups within pancreatic adenocarcinoma: quiescent, glycolytic, cholesterogenic,
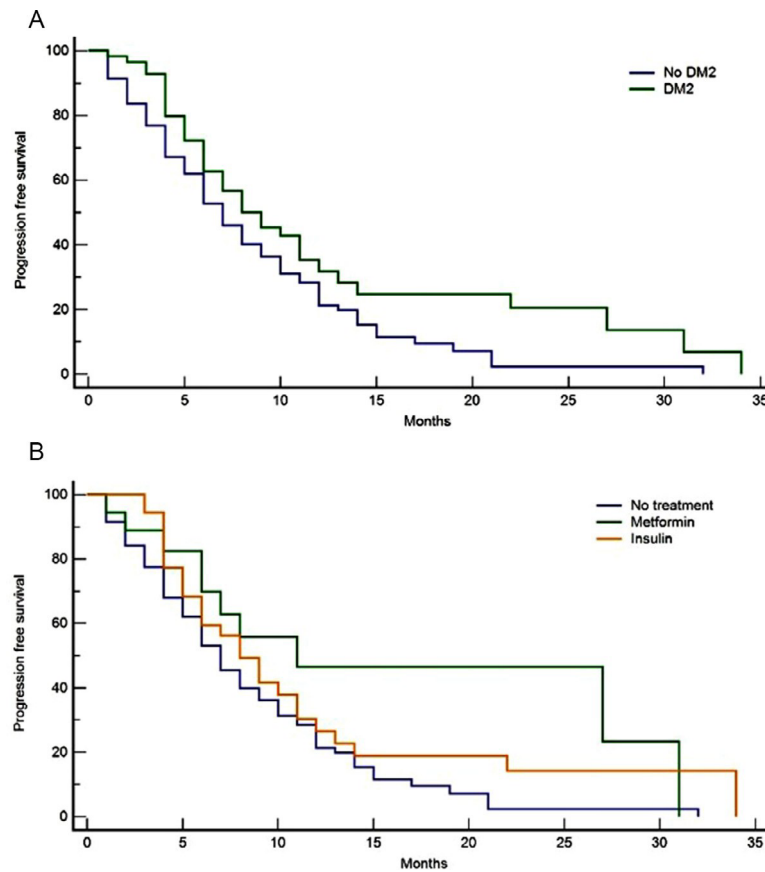
Fig. 2. A. 1st line progression free survival no type 2 DM versus treated type 2 DM; B. 1st line progression free survival in no DM2 versus insulin-treated DM2 versus metformin-treated DM2.

and mixed. Among them, the glycolytic subtype showed the shortest overall survival.

In this context, using antidiabetic drugs such as insulin and metformin may hinder the metabolic remodeling operated by cancer cells. Metformin is the most extensively studied drug in preclinical and clinical settings [56]; its activity occurs through several mechanisms. One of the main ones consists of inhibition of complex I of the mitochondrial electron transport chain, causing several effects, including energetic discomfort leading to activation of AMPK [57]. Other effects caused by this inhibition include reduction of mTOR signaling activity, which in turn inhibits cell proliferation, and inhibition of hepatic gluconeogenesis through blockade of pyruvate decarboxylase. In this way, cancer cells that have lost energy stress control and compensation systems are more susceptible to energy stress, leading to cell death [58].

The role of insulin is more controversial, as it is generally considered to favor metabolism and neoplastic proliferation. However, recent work has highlighted different results. Previously, Pretta et al., evaluated progression-free survival and overall survival in 164 patients (92 non-diabetic and 72 diabetics treated with insulin) with metastatic PDAC and treated with the same chemotherapy combination. Patients undergoing insulin treatment demonstrated higher PFS and OS on univariate and multivariate analyses [59]. The mechanisms underlying this different response can be explained by the study by Pircher et al., In which the influence of ADMs in patients with prostate cancer is investigated. The study highlighted a significant advantage in terms of overall survival in patients treated with insulin or metformin. According to the literature data, the authors probed the mechanisms of action of the two drugs on AMPK and mTOR, the two most implicated path-

ways. The levels of AMPK and mTOR activated by phosphorylation in specific amino acid residues were considered: phospho-AMPK-Thr172 (pAMPK) and phospho-mTORSer2448 (pmTOR). This led to the demonstration that insulin treatment can significantly reduce the activity levels of pmTOR in tumor tissue, thus reducing tumor growth and neoplastic tissue development [60].

The concentration of glucose and other metabolites (lactates and glutamine) in the tumor microenvironment (TME) also affect the activity of the immune system cells. In fact, cancer cells consume as much glucose as available to the detriment of immune system cells such as T cells, NK cells, macrophages, etc., reducing their activity and inhibiting antitumor immunity [61,62]. This occurs because the reduced availability of glucose in the tumor microenvironment (TME) limits and inhibits a series of fundamental processes for the activity of tumor-infiltrating lymphocytes (TILs), such as glycolysis, Ca2 + signaling, and the production of cytokines [63,64].

Restrictions on using nutrients in immune cells are apparently immunologically associated with tumors that do not undergo immune infiltration (so-called cold tumors). Furthermore, tumor-infiltrated immunosuppressive cells (Treg cells and MDSCs) and vascular endothelial cells tributary of the neoplastic cancer lesion also consume and deplete the nutrients in TME, contributing to an immunosuppressive environment. Treg cells in particular, act competitively against glucose, inducing replicative senescence of CD4 + and CD8 + T cells. The activity of TLR8 hinders the corresponding action of Treg cells, thus improving antitumor immunity. Furthermore, the Treg cells in TME convert ATP to adenosine, inhibiting the activity of immune cells in tumors [65–67]. A consequence of anaerobic glycolysis operated by cancer cells is the increased production of lactate, which, in turn, inhibits the activity

of immune cells, reducing the function of effector T cells. A similar function occurs with glutamine [68,69].

Furthermore, the inflammation itself is linked to the immuno-metabolic context since the pro-inflammatory stimulus can induce a metabolic switch in hematopoietic cells, increasing aerobic glycolysis in a similar way to the Warburg effect [70,71].

An interesting aspect is that insulin receptors are expressed in activated CD4 + T cells and can help remodel the adaptive immune system by regulating T-cell metabolism [72]. This condition is confirmed by the fact that in preclinical models of induced knockdown for insulin receptors, there was a reduced glucose metabolism and cytokine production by T cells [73].

The evaluation of these aspects would seem in line with the results of our work, which correlates metformin and insulin treatment in patients with DM2 with a better OS and a tendentially better PFS. The hypothesis is that metformin and insulin can inhibit tumor cell proliferation through a rebalancing of glucose metabolism that leads to cancer cell death and through reactivation of T lymphocytes and immune response against cancer cells. Ongoing trials investigate the activity of anti-diabetic medications ADMs and immuno-checkpoint inhibitors combination at preclinical and clinical levels. Among these, phase II study NCT03800602 evaluates the combination of nivolumab and metformin in MSS colorectal cancer; phase II study NCT04414540 analyzes the combination of pembrolizumab and metformin in head and neck cancers; and the study NCT03874000 which investigate the combination of sintilimab and metformin in NSCLC.

The study has limitations, including its retrospective nature, which involves several unavoidable biases, and the small sample size, which could be expanded in subsequent studies. In addition, in order to achieve the most realistic results possible, patients were over selected by a line of treatment, including only those treated with first-line gemcitabine-nab-paclitaxel combination; ECOG-PS, including 0 or 1 only; and excluding other comorbidities. The metabolic processes in pancreatic ductal adenocarcinoma are numerous and interconnected, representing a field still to be explored. For this reason, further studies and insights are needed in the future.

Conflict of interest

Prof. Scartozzi reports other from Amgen, other from Sanofi, other from MSD, other from EISAI, other from Merck, other from Bayer, outside the submitted work. Eleonora Lai has received advisory board and consultant fees from AstraZeneca and MSD. Mario Scartozzi has received consultant, advisory board and speakers' bureau fees from Amgen, Sanofi, MSD, EISAI, Merck, Bayer.

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Author contributions

All authors wrote and edited the manuscript.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.

[2] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694–705.

[3] Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569–78. doi:10.1016/S0140-6736(08)60269-X.

[4] Koorstra JB, Hustinx SR, Offerhaus GJ, Maitra A. Pancreatic carcinogenesis. Pancreatology 2008;8(2):110–25. doi:10.1159/000123838.

[5] American Diabetes AssociationDiagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–90.

[6] Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(Suppl 1):S5–S10. doi:10.2337/diacare.27.2007.s5.

[7] Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes 2017;66:1103–10. doi:10.2337/db16-1477.

[8] Li Y, Bian X, Wei S, He M, Yang Y. The relationship between pancreatic cancer and type 2 diabetes: cause and consequence. Cancer Manag Res 2019;11:8257–68. doi:10.2147/CMAR.S211972.

[9] Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann Oncol 2014;25:2065–72.

[10] Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer 2011;47:1928–37.

[11] Huxley R, Ansary-Moghaddam A, Berrington de Gonz_alez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076–83.

[12] Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. J Cell Biochem 2005;95(4):649–56. doi:10.1002/jcb.20461.

[13] Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. Nat Rev Cancer 2020;20(11):629–44. doi:10.1038/s41568-020-0295-5.

[14] Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 2015;95(3):727–48. doi:10.1152/physrev.00030.2014.

[15] Zhang AM, Wellberg EA, Kopp JL, Johnson JD. Hyperinsulinemia in obesity, inflammation, and cancer. Diabetes Metab J 2021;45(3):285–311.

[16] Bao B, Wang Z, Li Y, et al. The complexities of obesity and diabetes with the development and progression of pancreatic cancer. Biochim Biophys Acta 2011;1815:135–46. doi:10.1016/j.bbcan.2010.11.003.

[17] Duan X, Wang W, Pan Q, Guo L. Type 2 diabetes mellitus intersects with pancreatic cancer diagnosis and development. Front Oncol 2021;11:730038. doi:10.3389/fonc.2021.730038.

[18] Olson SH, Xu Y, Herzog K, Saldia A, DeFilippis EM, Li P, et al. Weight loss, diabetes, fatigue, and depression preceding pancreatic cancer. Pancreas 2016;45:986–91.

[19] Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134:981–7.

[20] Li D, Mao Y, Chang P, Liu C, Hassan MM, Yeung SJ, et al. Impacts of new-onset and long-term diabetes on clinical outcome of pancreatic cancer. Am J Cancer Res 2015;5:3260–9.

[21] Wróbel MP, Marek B, Kajdaniuk D, et al. Metformin - a new old drug. Endokrynol Pol 2017;68(4):482–96 indexed in Pubmed: 28819951. doi:10.5603/EP.2017.0050.

[22] Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev 2005 Jul 20(3):CD002966 Update in: Cochrane Database Syst Rev. 2015;9:CD002966. PMID: 1603488122. doi:10.1002/14651858.CD002966.pub3.

[23] Quoc Lam B, Shrivastava SK, Shrivastava A, Shankar S, Srivastava RK. The impact of obesity and diabetes mellitus on pancreatic cancer: molecular mechanisms and clinical perspectives. J Cell Mol Med 2020;24:7706–16. doi:10.1111/jcmm.15413.

[24] Bonelli L, Aste H, Bovo P, et al. Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in northern Italy. Pancreas 2003;27:143–9. doi:10.1097/00006676-200308000-00007.

[25] Ersoy C, Kiyici S, Budak F, et al. The effect of metformin treatment on VEGF and PAI-1 levels in obese type 2 diabetic patients. Diabetes Res Clin Pract 2008;81:56–60. doi:10.1016/j.diabres.2008.02.006.

[26] Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29(2):254–8. doi:10.2337/diacare.29.02.06.dc05-1558.

[27] Li D, Yeung SJ, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137(2):482–8.

[28] Baur DM, Klotsche J, Hamnvik OPR, et al. Type 2 diabetes mellitus and medications for type 2 diabetes mellitus are associated with risk for and mortality from cancer in a German primary care cohort. Metabolism 2011;60(10):1363–71.

[29] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. Am J Gastroenterol 2012;107(4):620–6.

[30] Ding XZ, Fehsenfeld DM, Murphy LO, Permert J, Adrian TE. Physiological concentrations of insulin augment pancreatic cancer cell proliferation and glucose utilization by activating MAP kinase, PI3 kinase and enhancing GLUT-1 expression. Pancreas 2000;21(3):310–20.

[31] Azar M, Lyons TJ. Diabetes, insulin treatment, and cancer risk: what is the evidence? F1000 Med Rep 2010;2(1).

[32] Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. Diabetes Metab Res Rev 2009;25(1):41–9. doi:10.1002/dmrr.v25:1.

[33] Gerstein HC, Bosch J, et al., ORIGIN Trial Investigators Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367(4):319–28.

[34] Chaitman BR, Hardison RM, Adler D, et al. The bypass angioplasty revascularization investigation 2 diabetes randomized trial of different treatment Strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. Circulation 2009;120(25):2529–40.

[35] Gerstein HC, Friedewald WT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358(24):2545–59.

[36] Patel A, MacMahon S, et al., Advance Collaborative Group Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358(24):2560–72.

[37] Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360(2):129–39.

[38] Gerstein HC, Miller ME, Genuth S, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364(9):818–28.

[39] Stefansdottir G, Zoungas S, Chalmers J, et al. Intensive glucose control and risk of cancer in patients with type 2 diabetes. Diabetologia 2011:1–7.

[40] Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W, Zhao G, Kip KE. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. Diabetes Care 2011;34:2323–8. doi:10.2337/dc11-0512.

[41] Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009;27:3297–302. doi:10.1200/JCO.2009.19.6410.

[42] Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 2008;8:915–28.

[43] Jeon CY, Li D, Cleary S, et al. The association of recently diagnosed diabetes and long-term diabetes with survival in pancreatic cancer patients: a pooled analysis. Pancreas 2018;47:314–20.

[44] Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg 2011;254:311–19.

[45] Bitterman DS, Winter KA, Hong TS, Fuchs CS, Regine WF, Abrams RA, Safran H, Hoffman JP, Benson AB 3rd, Kasunic T, Mulcahy M, Strauss JF, DiPetrillo T, Stella PJ, Chen Y, Plastaras JP, Crane CH. Impact of diabetes and insulin use on prognosis in patients with resected pancreatic cancer: an ancillary analysis of NRG oncology RTOG 9704. Int J Radiat Oncol Biol Phys Jan 2021;109(1):201–11. doi:10.1016/j.ijrobp.2020.08.042.

[46] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol Mar 1927;8(6):519–30 PMID: 19872213; PMCID: PMC2140820. doi:10.1085/jgp.8.6.519.

[47] de la Cruz-López KG, Castro-Muñoz LJ, DO Reyes-Hernández, García-Carrancá A, Manzo-Merino J. Lactate in the regulation of tumor microenvironment and therapeutic approaches. Front Oncol 2019;9:1143 PMID: 31737570; PMCID: PMC6839026. doi:10.3389/fonc.2019.01143.

[48] Buescher JM, Driggers EM. Integration of omics: more than the sum of its parts. Cancer Metab Feb 2016;4:4 PMID: 26900468; PMCID: PMC4761192. doi:10.1186/s40170-016-0143-y.

[49] Reznik E, Luna A, Aksoy BA, Liu EM, La K, Ostrovnaya I, Creighton CJ, Hakimi AA, Sander C. A landscape of metabolic variation across tumor types. Cell Syst Mar 2018;6(3) 301-313.e3Epub 2018 Jan 27. PMID: 29396322; PMCID: PMC5876114. doi:10.1016/j.cels.2017.12.014.

[50] Ying H, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sananikone E, Locasale JW, Son J, Zhang H, Coloff JL, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 2012;149:656–70.

[51] Yun J, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, Willson JK, Markowitz S, Zhou S, et al. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. Science 2009;325:1555–9.

[52] Lau AN, Li Z, Danai LV, Westermark AM, Darnell AM, Ferreira R, Gocheva V, Sivanand S, Lien EC, Sapp KM, et al. Dissecting cell-type-specific metabolism in pancreatic ductal adenocarcinoma. Elife 2020;9:e56782.

[53] Follia L, Ferrero G, Mandili G, et al. Integrative analysis of novel metabolic subtypes in pancreatic cancer fosters newprognostic biomarkers. Front Oncol 2019 Epub ahead of print Feb 27. doi:10.3389/fonc.2019.00115.

[54] Daemen A, Peterson D, Sahu N, McCord R, Du X, Liu B, Kowanetz K, Hong R, Moffat J, Gao M, et al. Metabolite profiling stratifies pancreatic ductal adenocarcinomas into subtypes with distinct sensitivities to metabolic inhibitors. Proc Natl Acad Sci USA 2015;112:E4410–17.

[55] Karasinska JM, Topham JT, Kalloger SE, et al. Altered gene expression along the glycolysis–cholesterol synthesis axis is associated with outcome in pancreatic cancer. Clin Cancer Res 2019 Epub ahead of print November 4. doi:10.1158/1078-0432.CCR-19-1543.

[56] Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. Am J Gastroenterol 2012;107:620–6.

[57] Choi YK, Park KG. Metabolic roles of AMPK and metformin in cancer cells. Mol Cells Oct 2013;36(4):279–87 Epub 2013 Jun 19. PMID: 23794020; PMCID: PMC3887985. doi:10.1007/s10059-013-0169-8.

[58] Madiraju AK, Qiu Y, Perry RJ, et al. Metformin inhibits gluconeogenesis via a redox-dependent mechanism in vivo. Nat Med 2018;24:1384–94. doi:10.1038/s41591-018-0125-4.

[59] Pretta A, Ziranu P, Puzzoni M, Lai E, Orsi G, Liscia N, Molinaro E, Mariani S, Riggi L, Rovesti G, Dubois M, Migliari M, Persano M, Saba G, Impera V, Musio F, Batzella E, Demurtas L, Pusceddu V, Astara G, Faloppi L, Casadei Gardini A, Andrikou K, Cascinu S, Scartozzi M. Retrospective survival analysis in patients with metastatic pancreatic ductal adenocarcinoma with insulin-treated type 2 diabetes mellitus. Tumori Dec 2021;107(6):550–5 Epub 2020 Nov 26. PMID: 33243068. doi:10.1177/0300891620976945.

[60] Pircher A, Zieher M, Eigentler A, et al. Antidiabetic drugs influence molecular mechanisms in prostate cancer. Cancer Biol Ther 2018;19:1153–61.

[61] Renner K, Singer K, Koehl GE, Geissler EK, Peter K, Siska PJ, Kreutz M. Metabolic hallmarks of tumor and immune cells in the tumor microenvironment. Front Immunol Mar 2017;8:248 PMID: 28337200; PMCID: PMC5340776. doi:10.3389/fimmu.2017.00248.

[62] Xia L, Oyang L, Lin J, Tan S, Han Y, Wu N, et al. The cancer metabolic reprogramming and immune response. Mol Cancer 2021;20:28. doi:10.1186/s12943-021-01316-8.

[63] Rangel Rivera GO, Knochelmann HM, Dwyer CJ, Smith AS, Wyatt MM, Rivera-Reyes AM, et al. Fundamentals of T cell metabolism and strategies to enhance cancer immunotherapy. Front Immunol 2021;12:645242. doi:10.3389/fimmu.2021.645242.

[64] Zhang M, Jin X, Sun R, Xiong X, Wang J, Xie D, et al. Optimization of metabolism to improve efficacy during CAR-T cell manufacturing. J Transl Med 2021;19:499. doi:10.1186/s12967-021-03165-x.

[65] Lindau D, Gielen P, Kroesen M, Wesseling P, Adema GJ. The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. Immunology 2013;138:105–15. doi:10.1111/imm.12036.

[66] Peixoto A, Relvas-Santos M, Azevedo R, Santos LL, Ferreira JA. Protein glycosylation and tumor microenvironment alterations driving cancer hallmarks. Front Oncol 2019;9:380. doi:10.3389/fonc.2019.00380.

[67] Haist M, Stege H, Grabbe S, Bros M. The functional crosstalk between myeloid-derived suppressor cells and regulatory T cells within the immunosuppressive tumor microenvironment. Cancers 2021;13:210. doi:10.3390/cancers13020210.

[68] Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell 2015;162:1229–41. doi:10.1016/j.cell.2015.08.016.

[69] Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. Cel Metab 2017;25:1282–12e7. doi:10.1016/j.cmet.2016.12.018.

[70] Palsson-McDermott EM, O'Neill LAJ. Targeting immunometabolism as an anti-inflammatory strategy. Cell Res 2020;30:300–14.

[71] Cao L, Wu J, Qu X, Sheng J, Cui M, Liu S, Huang X, Xiang Y, Li B, Zhang X, et al. Glycometabolic rearrangements–aerobic glycolysis in pancreatic cancer: causes, characteristics and clinical applications. J Exp Clin Cancer Res 2020;39:267.

[72] Helderman JH, Reynolds TC, Strom TB. The insulin receptor as a universal marker of activated lymphocytes. Eur J Immunol 1978;8:589–95.

[73] Fischer HJ, Sie C, Schumann E, Witte AK, Dressel R, van den Brandt J, Reichardt HM. The insulin receptor plays a critical role in T cell function and adaptive immunity. J Immunol 2017;198:1910–20.