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Source / Izvornik: **Diabetology, 2023, 4, 553 - 559**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.3390/diabetology4040049>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:184:421839>

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Download date / Datum preuzimanja: **2025-01-15**



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Commentary

Could Microbiome Be the Common Co-Denominator between Type 2 Diabetes and Pancreatic Cancer?

Marin Golčić ^{1,*}  and Andrej Belančić ^{2,3,*} 

¹ Department of Radiotherapy and Oncology, Clinical Hospital Centre Rijeka, Krešimirova 42, 51000 Rijeka, Croatia

² Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, Krešimirova 42, 51000 Rijeka, Croatia

³ Department of Basic and Clinical Pharmacology with Toxicology, Faculty of Medicine, University of Rijeka, Braće Branchetta 20, 51000 Rijeka, Croatia

* Correspondence: marin.golcic@gmail.com (M.G.); a.belancic93@gmail.com (A.B.)

Abstract: Similar microorganisms, via similar mechanisms, play a role in the development of both pancreatic cancer (PC) and type 2 diabetes (T2D). Since the new onset of T2D is potentially one of the earliest signs of PC, it is highly plausible that a common denominator might be responsible for both, as the growth of the cancer will take a longer time to manifest compared to the insulin resistance. Although a variety of host-dependent factors and susceptibility play a role, and the mechanisms connecting the two diseases remain poorly understood, future well-designed trials should hypothesize whether a microbial intervention (modification and/or transplantation) results in a lower incidence and the better treatment of both diseases since the T2D–PC–gut microbiome interconnection seems scientifically logical.

Keywords: chronic inflammation; diabetes mellitus type 2; microbiome; pancreatic cancer; tool-like receptors



Citation: Golčić, M.; Belančić, A. Could Microbiome Be the Common Co-Denominator between Type 2 Diabetes and Pancreatic Cancer? *Diabetology* **2023**, *4*, 553–559. <https://doi.org/10.3390/diabetology4040049>

Academic Editor: Peter Clifton

Received: 4 September 2023

Revised: 17 October 2023

Accepted: 28 November 2023

Published: 7 December 2023



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1. The Relationship between Diabetes and Pancreatic Cancer

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by hyperglycemia due to defective insulin secretion, the inability of insulin-sensitive tissues to respond appropriately to insulin, or both [1]. Due to its increasing incidence, T2DM is often referred to as the global epidemic of the 21st century, with an expected prevalence of 12.2% of the world's population by 2045 [2]. While the chronic health issues of T2DM are often associated with vascular complications, as almost 75% of all patients with coronary disease exhibit concomitant T2DM or abnormal glucose regulation [3], T2DM is also associated with a higher incidence of and worse overall survival (OS) for various cancers [4].

A particularly complex relationship exists between T2DM and pancreatic cancer (PC), the third leading cause of cancer death worldwide in men and women combined [5]. Despite the advances in modern oncology, the data from the largest phase III trials demonstrate a median OS of only 54 months after PC surgery [6] and 11.1 months after the diagnosis of metastatic PC [7]. Only several clinical trials with selected patient groups exhibited survival longer than 19 months in the metastatic setting [8]. Various factors influence the development of PC, including particular genetic drivers, family history, chronic pancreatitis, smoking, periodontal disease, drinking, and older age [9].

A long-standing T2DM is also associated with both the development of PC, with a relative risk of 2.1 (95% CI: 1.6–2.8) [10], and with a higher mortality of PC, particularly in patients with resectable cancer (HR: 1.37; 95% CI: 1.15–1.63) [11]. The relationship between the two diseases appears to be bidirectional as new-onset T2DM is associated with a significantly increased rate of PC diagnosis, particularly in the first 2 years after T2DM diagnosis (hazard ratio of 2.2 (95% CI 1.84–2.56)) [12]. On the other hand, removing both cancerous and normal pancreatic tissue after PC surgery improves related diabetic

symptoms despite the loss of insulin-secreting tissue [13]. Hence, the data suggest that T2DM can both be part of the pathogenesis of PC and an early symptom and consequence of PC.

Despite the significant prevalence of both diseases, the data elucidating such a complex and bidirectional relationship are relatively scarce. For example, due to insulin resistance, an increase in insulin signaling pathways and insulin-like growth factor-1 (IGF-1) levels in T2DM can also lead to the proliferation and inhibition of apoptosis in PC, as IGF-1 receptors are usually highly expressed in PC cells [14,15]. Furthermore, T2DM is characterized by hyperglycemia, which does not increase neoplastic growth but can trigger oxidative stress, a factor in cancer pathogenesis. Additionally, several tumor-secreting products and metabolites such as amino acids, bile acids, and sphingolipids have been shown to be increased in PC after new-onset T2DM and could all play a role in PC development. On the other hand, developing paraneoplastic syndromes in PC can lead to insulin resistance [14].

Understanding the relationship between PC and T2DM in more detail could lead to earlier diagnosis and better treatment outcomes for both diseases. Hence, it is crucial to undertake research examining whether there is a common denominator linking both diseases. In this commentary, we suggest that the relationship between T2DM and PC should not only be looked at as bidirectional, as there is another significant factor at the root of both diseases, demonstrating a trilateral relationship—the microbiome.

2. The Importance of Microbiome in Pancreatic Cancer and Diabetes Mellitus

The microbiome comprises bacteria, archaea, viruses, and eukaryotes, which impact the metabolic and immune functions of the human body [16]. It has long been known that some of the bacteria in the gut microbiome can cause cancer, such as *Helicobacter pylori*, first identified in 1982 by Robin Warren and Barry Marshall [17], while other components of the microbiome have anti-tumoral potential [18]. While it was long thought that tumors are sterile, researchers have demonstrated the presence of microbiome in the tumoral milieu; this includes *H. pylori* DNA, which was found in 60% of patients with PC, suggesting that *H. pylori* may play a role in the occurrence of PC [19]. However, there are also data showing a higher prevalence of *H. pylori* infection in diabetic obese patients compared to nondiabetic patients (23.6% vs. 11.8%, $p < 0.001$) [20], suggesting that T2DM is a predisposing factor for the infection [21] and that the bacterium may be able to play its pathogenic role in the whole disease process [22].

A landmark study by Pushalkar et al. detected specific gut and tumor microbiomes in murine PC models, suggesting that a potential bacterial translocation can occur from the intestinal tract into the peritumoral setting [23]. Following these data, Riquelme et al. demonstrated that certain gut bacterial strains and a high microbial diversity can predict survival in patients with PC [24]. Furthermore, the same authors showed that fecal microbial transplantation (FMT), a method of impacting the whole host–microbiome ecosystem with capsules or an endoscopy from a particular donor, could modulate or shift the overall intratumoral bacterial composition. The performed FMT on the murine model demonstrated that applying the donor gut microbiota can influence tumor microbiota, tumor growth, and the level of CD8+ cells, the effects of which could be annulated by antibiotics. The effect shown was, in minor part, caused by direct translocation into the tumor through the bile duct and, more significantly, by altering the gut microbial landscape, shaping the immune response and promoting T-cell activation [24].

Dysbiosis of the gut microbiome also plays a significant role in T2DM. Qin et al. performed a metagenome-wide association study in 2012 in T2DM patients, demonstrating the presence of moderate intestinal dysbiosis characterized especially by a decrease in butyrate-producing bacteria and an increase in various opportunistic pathogens [25]. A Danish study evaluating the serum metabolome of insulin-resistant individuals found that dysbiosis of the human gut microbiome impacted the serum metabolome, systemic immunity, and contributed to insulin resistance [26]. FMT was also used in T2DM patients, showing that the colonization of the donor-derived microbiome via FMT could significantly

improve insulin resistance, body mass index, and other clinical indicators in T2DM patients. FMT resulted in an improved microbial richness and Shannon diversity in the intervention group, while the relative abundance of Bacteroidetes was decreased and that of Firmicutes was increased after the intervention with FMT [27].

Oral microbes also play an important role in both PC and T2DM pathogenesis. Bacteria such as *Porphyromonas gingivalis* are important contributors to periodontal disease and may cause systemic inflammation. However, *P. gingivalis* is also shown to be associated with PC, as a comparison of PC patients and healthy controls demonstrated that higher levels of antibodies against a pathogenic strain of *P. gingivalis* were associated with a higher risk of developing PC (RR 2.14; 95% CI, 1.05–4.36) [28]. A similar effect was registered for *Fusobacterium nucleatum*, another periodontal pathogen [29]. On the contrary, higher levels of antibodies against commensal oral bacteria were associated with a 45% lower risk of PC when compared to those with lower levels of antibodies (RR 0.55; 95% CI, 0.36–0.83), suggesting that the presence of certain oral bacteria may actually decrease the risk of PC [28]. However, *P. gingivalis* is also shown to play an important role in the development of insulin resistance in mice fed with a high-fat diet through the synthesis of branched-chain amino acids [30]. Similarly, *F. nucleatum* levels are also positively correlated with fasting blood glucose and glycated hemoglobin, resulting in insulin resistance [31], demonstrating the role of oral pathogens in both T2DM and PC pathophysiology.

Along with gut bacteria, specific fungal microorganisms have also been associated with both diseases. *Malassezia*, the most prevalent fungal genus in PC, have been associated with the accelerated growth of PC via mannose-binding lectin, a soluble recognition molecule that binds to the terminal sugar residues present on the surface of microorganisms [32]. However, *Malassezia* is also implicated in T2DM, as the data show a high prevalence of *Malassezia* in patients with T2DM, with a lower number of yeasts in patients with adequate glycemic control [33].

3. Molecular Basis for the Trilateral Relationship

There are various mechanisms through which the microbiome can influence the development of both PC and T2DM. For example, microbial products such as short-chain fatty acids (SCFA) are dysregulated in PC, leading to the activation of the NF- κ B signaling pathway, which can downregulate p53 expression and the level of inflammation [34]. A positive correlation between SCFA levels and a longer progression-free survival in patients with solid tumors were also registered in various studies [35]. On the other hand, Zhao et al. demonstrated that there is also a difference in the concentrations of microbiome and SCFA between healthy controls and T2DM patients. While the abundances of certain SCFA-producing bacteria were significantly increased in T2DM patients, the fecal SCFA concentrations were significantly decreased [36], which is important since SCFA butyrate can also provide a beneficial role in b-pancreatic cell function, as opposed to SCFA propionate which has a detrimental effect on diabetes risk [37].

The microbiota in diabetic patients also exhibited an increase in the oxidative stress response, potentially a direct link to the pro-inflammatory state of patients with T2DM. Moreover, diabetic subjects presented higher fasting and postprandial LPS concentrations than lean nondiabetic or obese subjects due to increased intestinal permeability [38]. Through a neuroendocrine pathway, increased gut permeability in T2DM patients can spread bacteria to other parts of the body. While the normal gut microbiota can dampen the nervous system's stress response, dysbiosis can result in an exaggerated hypothalamic–pituitary–adrenal reaction to stress, leading to an increased cortisol release and dysfunction of the gut barrier [38]. Parekh et al. previously showed that one of the earliest changes detectable in the evolution of T2DM is abnormalities in autonomic balance, which could be influenced by the gut microbiome [39].

Chronic inflammation and the response through toll-like receptors (TLRs) appear to be the central aspects linking T2DM, PC, and the microbiome. Chronic inflammation is associated with a phenotypic pro-inflammatory shift in bowel lamina propria immune cell

populations [40] and the activation of different TLRs, which are innate immune sensors that recognize various stimuli and can both respond to invading pathogens and also regulate inflammatory responses and maintain epithelial barrier homeostasis.

TLRs have a complex relationship with carcinogenesis, as TLR4 and TLR7 are over-expressed by PC cells in both mice and humans, and exogenous TLR ligands can lead to accelerated pancreatic carcinogenesis in models of acute and chronic pancreatitis [41]. However, some TLR signaling pathways are tumor-suppressive, and due to a high degree of complexity and crosstalk with other signaling pathways, the overall outcome of TLR manipulation may not be easily predictable [42].

TLR4s are also expressed in insulin target tissues and are an important mediator of insulin resistance through activation by exogenous ligands, such as dietary fatty acids and enteric lipopolysaccharide, and endogenous ligands, such as free fatty acids, which are elevated in obese states. TLR4 activates the pro-inflammatory kinases that impair insulin signal transduction directly through the inhibitory phosphorylation of the insulin receptor substrate on serine residues and also leads to the increased transcription of pro-inflammatory genes, resulting in the elevation of cytokine, chemokine, reactive oxygen species, and eicosanoid levels; these promote further insulin desensitization within the target cell itself and in other cells via paracrine and systemic effects [43].

The microbiome exerts at least part of its physiological functions through TLRs, which means that the bacteria can potentially influence the pathogenesis of both PC and T2DM through the same pathways. Pulshakar et al. showed that various TLRs (3,4,7, and 9) are upregulated in PC, and that their activation accelerates oncogenesis via the induction of innate and adaptive immune suppression. Furthermore, the authors demonstrated that a distinct microbiome drives suppressive monocytic cellular differentiation in PC via selective TLR ligation leading to T-cell anergy, showing proof that the tumor-promoting effects of the PC microbiome are TLR dependent [23]. It was also shown that at least some of the carcinogenic effects of the oral bacterial strain *F. nucleatum* are due to TLR4 signaling, which can lead to the activation of the nuclear factor NFκB [44]. *F. nucleatum* has also been shown to induce cytokine release via the TLR2 signaling pathway, while also correlating with blood glucose and glycated hemoglobin levels [31]. Even fungal microorganisms such as *Malassezia* exert their function at least partially through TLRs, although specific data regarding T2DM and PC are lacking [45].

The relationship of the microbiome with both T2DM and type 1 diabetes is also regulated through the TLR signaling pathway [46], of which type 4 TLR-LPS signaling is particularly important and has been shown to mediate the metabolic benefits of caloric restriction [47]. It has also been shown that the deletion of TLR4 is associated with a higher abundance of Bacteroidetes and a lower abundance of Firmicutes in the large intestine, along with lower levels of circulating SCFA. Clinically, the deletion of TLR4 also results in insulin-resistance-related abnormalities in the energy metabolism [48].

4. Microbiome—The Common Denominator?

The data show that T2DM and PC patients exhibit signs of microbial dysbiosis. Although the relationship between T2DM and PC is likely bidirectional, complex, and multi-causal, the finding that the new onset of T2DM is potentially one of the earliest signs of pancreatic cancer suggests that a common denominator might be responsible for both, as the growth of the cancer will take a longer time to manifest compared to the insulin resistance.

Evidence suggests that certain pathological bacterial strains can influence the development of both diseases, primarily through TLRs, which suggests that the microbiome might be a common denominator between the two diseases. Of course, various host-dependent factors and biological susceptibility play a role, and the mechanisms connecting the two diseases remain poorly understood. However, future trials could help to demonstrate the potential use of the microbiome as a screening tool, particularly for the oral microbiome, and could help to detect PC in earlier stages. Furthermore, we hypothesize that a microbial intervention might result in a lower incidence and better treatment of both diseases.

Author Contributions: M.G. and A.B. contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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