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ASSOCIATION OF DIABETES MELLITUS TYPE 2 AND ANTIDIABETIC DRUGS WITH PANCREATIC CARCINOMA: A LITERATURE REVIEW

ASSOCIAÇÃO DA DIABETES MELLITUS TIPO 2 E DOS FÁRMACOS ANTIDIABÉTICOS COM O CÂNCER PANCREÁTICO: UMA REVISÃO DE LITERATURA

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ABSTRACT

Pancreatic cancer has a high mortality rate and its diagnosis has often been associated with that of type 2 diabetes mellitus (DMT2), although the pathophysiological mechanisms of this relationship still require clarification. Thus, the aim of this study is to analyze aspects of the association between DMT2 and its pharmacological therapy with the development of pancreatic carcinoma. To this purpose, a thorough search of the literature published between 2015 and 2020 in electronic health databases was carried out, and, after the selection process, 13 articles on BHS and 14 on PUBMED were included in this study. In summary, the inflammatory characteristic of DMT2, hyperinsulinemia and insulin resistance are pathophysiological hypotheses of the association. Furthermore, the relationship between long-term diabetes and the development of carcinoma is significant, although recent onset diabetes is also demonstrated to be relevant. In addition, the association between antidiabetic drugs and pancreatic cancer is assessed. In this regard, some drugs, such as metformin, are associated with antitumor effects. In contrast, incretins are related to carcinogenesis, due to their potential deleterious effects on the pancreas. In parallel, insulin can amplify the relationship between hyperinsulinemia and the risk of malignancy, as well as drugs such as sulfonylureas, which are associated with an increased risk of cancer for causing abnormal stimulation of cell proliferation.

Keywords: Adult. Diabetes Mellitus Type 2. Pancreatic neoplasms.

RESUMO

O câncer de pâncreas possui alta taxa de mortalidade e, com frequência, seu diagnóstico tem sido associado ao de diabetes mellitus tipo 2 (DMT2), embora os mecanismos fisiopatológicos dessa relação ainda necessitem de esclarecimentos. Dessa forma, o objetivo deste estudo é analisar os aspectos da associação entre a DMT2 e sua terapia farmacológica com o desenvolvimento de carcinoma pancreático. Para este fim, realizou-se uma busca criteriosa da literatura publicada entre 2015 e 2020 em bases de dados eletrônicas em saúde, e, após o processo de seleção, 13 artigos na BVS e 14 na PUBMED foram incluídos neste estudo. Em suma, a característica inflamatória da DMT2, a hiperinsulinemia e a resistência à insulina são hipóteses fisiopatológicas da associação. Outrossim, é significativa a relação da diabetes de longa duração com o desenvolvimento do carcinoma, apesar de a diabetes de início recente também demonstrar-se relevante. Ademais, a associação entre medicamentos antidiabéticos e câncer de pâncreas também é avaliada. Sob esse viés, alguns medicamentos, como a metformina, estão associados a efeitos antitumorais. Em contrapartida, as incretinas estão relacionadas à carcinogênese, devido aos seus potenciais efeitos deletérios no pâncreas. Em paralelo, a insulina pode amplificar a relação entre hiperinsulinemia e o risco de malignidade, assim como drogas como as sulfonilureias, que estão associadas ao risco aumentado de câncer por provocar estimulação anormal da proliferação celular.

Palavras-chave: Adulto. Câncer de pâncreas. Diabetes Mellitus Tipo 2.

INTRODUCTION

According to Tan *et al*. (2017), pancreatic cancer is one of the most lethal neoplasms, with a five-year relative survival rate below 5% (BEN, 2011; TAN *et al.* 2017). Moreover, most patients are diagnosed at a late stage, precluding surgery with curative intent (BEN, 2011). These factors highlight the need for understanding the pathophysiological mechanisms and risk factors of pancreatic cancer, aiming to reduce mortality among patients.

In this sense, different studies have addressed the association between pancreatic cancer and type 2 diabetes mellitus (T2DM), not only because it is one of the most common diseases in the world (INTERNATIONAL DIABETES FEDERATION, 2019), but also because epidemiological studies have verified a high incidence of pancreatic cancer in people diagnosed with diabetes (ANDERSEN, 2017). According to the International Diabetes Federation (IDF), 9.3% of the world population aged 20–79 years (463 million people) was estimated to be living with diabetes in 2019 – a condition characterized by sustained hyperglycemia resulting from defects in insulin action (IDF, 2019). Besides causing target organ damage, this metabolic alteration seems linked to carcinogenesis (CARRERAS-TORRES, 2017; TAN *et al.,* 2017).

Although not fully established (ANDERSEN, 2017), different authors formulated hypothesis about the pathophysiological mechanisms that link diabetes to the development of malignant neoplasms in the pancreas. We may mention, for example, the proportionality of HbA1c levels, as well as hyperinsulinemia and insulin resistance as essential for damaging the pancreas and increasing insulin production, which corroborates for carcinogenesis (LU *et al*., 2015). However, the implication of diabetes in individual predisposition to cancer is not clarified, nor whether this metabolic alteration would be a consequence of the malignant tumor (WOJCIECHOWSKA, 2016).

The association between diabetes and cancer development was explained by different hypotheses, such as the use of antidiabetic drugs. Some drugs, such as the metformin, are associated with anticancer effects (JANG *et al.,* 2017). In turn, incretins may manifest adverse effects on the pancreas (AZOULAY *et al.,* 2016), and insulin may drives hyperinsulinemia – both associated with cancer risk (LEE *et al.,* 2018). This is also the case of sulphonylurea drugs, which are associated with increased risk of cancer for causing abnormal cell proliferation (VALENT, 2015).

Being two diseases of public health significance, thoroughly understanding their association is important. Thus, this study aims to perform a literature review on researches describing aspects of T2DM and its pharmacological therapy that may be associated with the development of pancreatic cancer.

METHODOLOGY

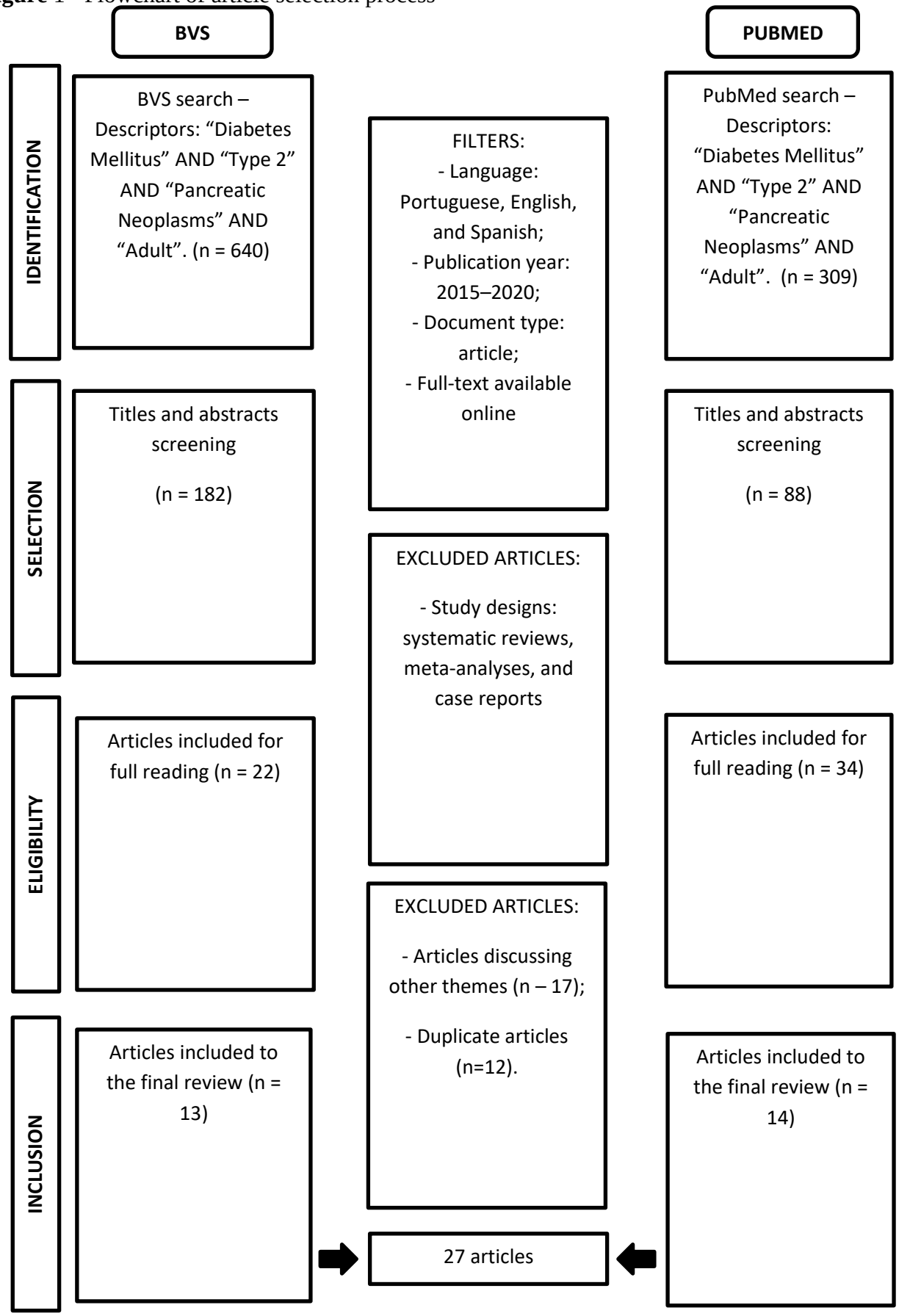
This study consists of a literature review on the association between pancreatic cancer and type 2 diabetes mellitus and its drug therapy. To this end, a search was conducted in the National Library of Medicine (PUBMED) and the Virtual Health Library (BVS) databases for scientific articles relevant to the subject, using the English counterparts of the descriptors “Diabetes mellitus tipo 2”, “Neoplasias Pancreáticas,” and “Adultos,” determined using the Exchange Index Query of the Health Sciences Descriptors (DECS) platform of the Virtual Health Library, namely: “Diabetes Mellitus", "Type 2,” “Pancreatic Neoplasms,” and “Adult.”

The descriptors were associated with the Boolean operator AND, resulting in the following search pattern: “Diabetes Mellitus” AND “Type 2” AND “Pancreatic Neoplasms” AND “Adult”.

The search was conducted between September 6, 2020 and January 12, 2021, including articles available online, in full, published from 2015 to 2020, in Portuguese, English, and Spanish.

The collected articles were analyzed by the screening of titles and abstracts, selecting the literature related to the proposed theme so that, later, they could be read in full. Duplicate articles were excluded from the sample, as well as systematic reviews, meta-analyses, and case reports. Figure 1 shows the details of our research methodology.

Figure 1 - Flowchart of article selection process



Source: the authors.

DEVELOPMENT

Epidemiology of Pancreatic Cancer

Epidemiological studies indicate that cancer death rates are higher among patients with T2DM when compared to the general population. In a retrospective study on cancer incidence and mortality among patients with T2DM conducted by Gu *et al.* (2016) in Shanghai, China, the authors found pancreatic cancer to have the highest incidence and mortality rates in both genders, verifying no significant difference between genders as to incidence. In another retrospective study conducted by He, Shi, and Wu (2018), investigating the association between T2DM and cancer in a Chinese population, the authors found patients with long-lasting diabetes to present a higher risk of pancreatic cancer.

Main pathophysiological aspects of the association between diabetes mellitus and pancreatic cancer

T2DM is an adult-onset metabolic disorder associated with an increased risk for different types of malignant neoplasms, including pancreatic cancer (DAI *et al.,* 2016). However, despite the evidence on the association between T2DM and pancreatic cancer, its pathogenesis is still little known (MUELLER *et al.*, 2019). The first hypothesis suggests that new-onset diabetes is a paraneoplastic phenomenon caused by diabetogenic products secreted by the tumor itself, such as the S-100A8N-terminal peptide, adrenomedullin, and exosomes (DUGNANI *et al.*, 2016). Lu *et al.* (2015) assign such an association to high HbA1c levels, citing hyperinsulinemia and insulin resistance as key factors for this. This hypothesis corroborates the understanding that the damage to the pancreas and the consequent increase in insulin secretion as a means to counteract insulin resistance are pathophysiological factors directly linked to the development of neoplasia. Increases in fasting blood sugar levels raise the cumulative risk of pancreatic cancer in both diabetic and prediabetic patients (KOO *et al.*, 2019).

Still regarding the mechanisms that may lead to pancreatic cancer development, Antwi *et al.* (2016) address the role of inflammation in this cancer pathogenesis. As T2DM is an inflammatory disease, this mechanism may explain such pathophysiological association, for inflammatory mediators related to visceral obesity are released before T2DM development in overweight patients.

Finally, studies have reported an association between increased glucose, glucagon, and pancreatic cancer, whereby glucagon levels drop with increasing blood sugar levels in healthy individuals, whereas those with T2DM show no such association. Similarly, patients with pancreatic cancer respond to glucose with increased glucagon levels, which may constitute an important physiological finding to understand this association (STERN *et al.,* 2019). Thus, several mechanisms seem to be involved in the association between T2DM and pancreatic cancer, including insulin resistance and inflammatory factors.

Duration of type 2 diabetes mellitus and pancreatic cancer

Using data obtained by the Biospecimen Resource for Pancreas Research, Antwi *et al.* (2016) verified that diabetes mellitus is associated with increased risk for pancreatic cancer, especially among individuals with long-lasting diabetes (≥ 5 years). This finding corroborates that reported by He, Shi, and Wu (2018).

Moreover, the literature also indicates that new-onset diabetes can precede cancer diagnosis by up to three years (RISCH *et al.*, 2017). In a study conducted by Dong *et al.* (2018) on the co-occurrence of pancreatic cancer and diabetes, the authors found the latter pathology to be classified as being of new onset in most of the patients, thus endorsing the chronological classification of diabetes as a risk factor for pancreatic cancer. In this scenario, plasma concentrations of glucose-

dependent insulinotropic peptide and pancreatic polypeptide may indicate that insulin resistance corroborates the development of diabetes associated to pancreatic cancer (ŠKRHA *et al.*, 2017). Although peptides are not tangentially related to diabetes, new-onset diabetes appears as a possible predictive of cancer development when associated with weight loss (ŠKRHA *et al.*, 2017).

We should also mention that, despite being associated with cancer development, diabetes duration is not significantly associated with the size, stage, or location of the tumor (body or tail of the pancreas) (DUGNANI *et al.*, 2016).

Association between the pharmacological treatment for type 2 diabetes mellitus and pancreatic cancer

The association between diabetes and cancer development was explained by different hypotheses, such as the use of antidiabetic drugs. Whereas some drugs, such as metformin (an insulin sensitizer), have been associated with reduced cancer incidence, insulin and sulphonylurea drugs (insulin secretagogues) have been associated with increased cancer risk. Thus, studies have approached hyperinsulinemia as one of the factors through which diabetes and antidiabetic drugs may influence cancer risk – even though the exact mechanism is yet unknown (VALENT, 2015).

Currently, pharmacological treatments for T2DM include some older drugs such as metformin, sulphonylurea, and insulin, as well as recent ones, such as dipeptidil peptidase-4 (DPP4) inhibitor and thiazolidinedione (TZD) (AMIN *et al.*, 2016).

The literature on the theme has not yet reached a consensus regarding the association between antidiabetic drugs and pancreatic cancer, possibly due to divergencies in the studies designs, definitions, or drugs used for comparison purposes (LU *et al.*, 2015).

Metformin

Metformin is the most prescribed glucose-lowering medicine worldwide and a first-line treatment for type 2 diabetes (FROUWS *et al.*, 2017). This drug has been clinically associated with antitumor effects, preventing the development of tumors and slowing the progress of certain types of cancers. With regard to pancreatic cancer, preclinical studies ascertain metformin ability to inhibit tumorigenesis (JANG *et al.*, 2017), whereas some clinical studies have presented conflicting results regarding its effects (VALENT, 2015; AMIN *et al.*, 2016; LEE *et al.*, 2016; FROUWS *et al.*, 2017; JANG *et al.*, 2017; KAUTZKY-WILLER; THURNER; KLIMEK, 2017; LEE *et al.*, 2018).

In a cohort study conducted with 1,847,051 patients in Austria during 2006 and 2007, Kautzky-Willer, Thurner, and Klimek (2017) found metformin and statins to have a protective effect for pancreatic cancer. Likewise, in a study conducted with 1,916 individuals in the United States, Amin *et al.* (2016) found metformin to have a protective effect on metastatic and non-metastatic disease, showing that the risk of mortality was 12% lower among patients treated with the drug when compared to those treated with other drugs. These results are in line with a retrospective study conducted by Lee *et al*. (2014) with 237 patients treated between May 2005 and December 2013 in South Korea, where metformin exposure was associated with favorable survival outcomes in patients with pancreatic cancer and pre-existing T2DM, especially those at an advanced stage of the disease.

In a retrospective population-based cohort study conducted with 5,432 participants, Valent (2015) reported that metformin was the only medication significantly associated with decreased risk of pancreatic cancer among individuals with type 2 diabetes. In another cohort study with 1,919 patients between 2005 and 2011, Jang *et al.* (2017) concluded that metformin can decrease cancer-specific mortality rates of patients with resectable pancreatic cancer and pre-existing diabetes through dose–response relationship, regardless of other factors. Finally, Lee *et al.* (2018) also associated the use of metformin with reduced risk of pancreatic cancer.

These findings contradict those reported by Frouws *et al.* (2017), who, in a retrospective cohort study with 907 patients, found no association between metformin use and overall survival in

patients with pancreatic cancer. However, for the drug to directly act on cancer cells, effective concentrations of metformin must reach the neoplastic tissue, which may not have occurred with the dose used in the study.

Metformin is an antihyperglycemic agent that reduces hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis; improve peripheral insulin sensitivity; and slows intestinal glucose absorption (SONG, 2016; FROUWS *et al.*, 2017). Although animal models show that metformin may inhibit the proliferation of pancreatic cancer cells, other studies suggest that metformin effect on cancer is actually systemic, improving patients' metabolic profile rather than having a direct effect on tumor cells (CIFARELLI *et al.*, 2015; FROUWS *et al.*, 2017).

Experimental studies showed that metformin disrupts crosstalk between insulin receptor and other growth factor signaling systems in human pancreatic cancer cells (LU *et al.*, 2015). Moreover, it also lowers insulin and insulin-like growth factor 1 (IGF-1) levels, thus inhibiting the growth of pancreatic duct adenocarcinoma (PDAC) cells. Both insulin and IGF-1 stimulate neoplasia through its interaction with G-protein-coupled receptors, which promotes mitogenic signaling. Metformin also directly inhibits proliferation of PDAC cells by activating the AMP-activated protein kinase, which in turn inactivates the target-of-rapamycin – a regulatory pathway that promotes proliferation (AMIN *et al.*, 2016).

Incretins

Incretins are relatively new medicines for the treatment of T2DM, with a lower associated risk of hypoglycaemia and favorable effects on body weight. However, studies explore the possibility of this medicine being associated with the development of pancreatic cancer (AZOULAY *et al.*, 2016) due to its potential deleterious effects on the pancreas, for incretin-based agents act directly on this organ (TSENG *et al.*, 2017).

Incretin agents induce alterations related to pancreatic cancer, such as increased pancreatic mass, inflammation, pancreatic acinar and ductal cells proliferation, apoptosis inhibition, enhanced β-cell proliferation, and chronic pancreatitis. Different studies investigated the potential biological mechanisms through which incretins may induce or advance pancreatic cancer from the aforementioned alterations. Research with animal models have proposed three GLP-1-induced pathways: β-cell proliferation, β-cell apoptosis inhibition, and increased differentiation of adult stem cells in the ductal pancreatic epithelium (KNAPEN *et al.*, 2016).

However, these findings are not corroborated by research with human subjects. In an international multicenter cohort study with 972,384 patients followed between 2007 and 2014, Azoulay *et al.* (2016) found that incretin-based drugs are not associated with an increased risk of pancreatic cancer compared to sulphonylureas. Similarly, in a retrospective population-based cohort study conducted with 13,171 patients in China, Tseng *et al.* (2017), demonstrated that incretin-based therapy has no association with adverse pancreatic events in patients with T2DM. This finding supports the safety of this drug class regarding short-term risk of developing pancreatic cancer, although an in-depth analysis is required after long-term follow-up. The retrospective population-based cohort study conducted by Knapen *et al.* (2016) with 182,428 patients also reported no association between incretin use and pancreatic cancer after adjustment for indicators of T2DM severity.

Among incretin-based drugs, two classes were recently approved for T2DM treatment, namely: GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (TSENG, 2016).

Regarding DPP-4 inhibitors, we highlight the sitagliptin – probably the most used among the currently available drugs from this class (TSENG, 2016). However, studies have reached conflicting results as to its association with pancreatic cancer. Tseng (2016) conducted a retrospective cohort study with 71,137 sitagliptin users and 933,046 non-users, finding a significantly higher overall risk of pancreatic cancer among individuals who use the drug. The author warns that the study findings should not be extrapolated to other incretins without further confirmation. In turn, a study conducted

by Buse *et al.* (2017) with 14,671 participants showed the opposite: sitagliptin treatment led to fewer cases of pancreatic cancer when compared to treatment using placebo, although not statistically significant.

Insulin

Insulin-based therapies have been associated with an increased risk for pancreatic cancer (LEE *et al.,* 2018). This occurs because subcutaneous insulin injection may induce higher systemic insulin levels than endogenous insulin secretion, thus increasing insulin binding to the IGF-I receptor and, consequently, the association between hyperinsulinemia and malignancy risk (LIN *et al.,* 2015).

In a study conducted by Kautzky-Willer, Thurner, and Klimek (2017), the authors verified that patients treated with insulin presented an increased risk for pancreatic cancer, especially females. Lee *et al*. (2018) also found insulin treatment to be linked to an increased risk of pancreatic cancer. In a study conducted with 1,916 individuals with pancreatic adenocarcinoma and pre-existent diabetes mellitus, Amin *et al.* (2016) found insulin-treated patients to have a worse survival than patients treated without insulin.

Sulphonylureas

The effects of sulphonylurea therapy on cancer development are still debatable, evincing the need for further research to clarify such association (VALENT, 2015).

In a study conducted by Valent (2015), sulphonylureas use was significantly associated with a reduced risk of pancreatic cancer. Conversely, both in a study conducted by Kautzky-Willer, Thurner, and Klimek (2017) and in a population-based cohort by Lee *et al*. (2018), sulphonylurea therapy was associated with an increased risk for pancreatic cancer.

This may occur because sulphonylureas increase the activity of insulin-like growth factor-1 (IGF-1), causing abnormal stimulation of signaling cascades and enhancing growth factor-dependent cell proliferation, thus affecting cell metabolism (LEE *et al.,* 2018).

CONCLUSION

This literature review investigated the association between type 2 diabetes mellitus and pancreatic cancer. Although no consensus has been reached, different studies have formulated hypothesis that try to explain the pathophysiological mechanisms underlying this association, such as insulin resistance and inflammatory factors.

The influence of diabetes duration on pancreatic cancer onset has also been investigated, but without common understanding. Whereas in some studies long-lasting diabetes showed a significant impact on the association, others found new-onset diabetes to be more relevant.

Despite the lack of consensus among studies, a rather pertinent hypothesis is the influence of antidiabetic drugs on the development of pancreatic cancer. Drugs such as metformin are associated with antitumor effects; in turn, incretins demonstrate potential deleterious effects on the pancreas, regardless of the benefits exposed throughout this review. Insulin and sulphonylureas are associated with increased cancer risk, although the second drug class entails considerable controversies.

These findings indicate that there is still much to be clarified on the subject, indicating the need for complementary studies investigating the pathophysiological and chronological association between pancreatic cancer and type 2 diabetes mellitus, as well as the pathways that explain this carcinoma link with antidiabetic drugs.

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