TYPE 2 DIABETES MELLITUS AND CANCER: CARCINOGENESIS AND PROTECTIVE EFFECT OF ANTIDIABETIC DRUGS

Diabetes Mellitus tipo 2 e câncer: Carcinogênese e efeito protetor dos fármacos antidiabéticos

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Abstract: Recent epidemiological evidence suggests that the type 2 diabetes mellitus, which accounts for 90% of all diabetics in the world, is closely linked to the increased incidence of certain types of cancer such as pancreas, breast, ovarian, endometrial, liver, colon, stomach and skin. Furthermore, it determines unfavorable evolution in these cases, increasing the mortality of patients simultaneously affected by such diseases, when compared to non-diabetic patients with some type of cancer. Well-designed studies also demonstrate the existence of a protective relationship, as much for the development as for progression of these cancers, provided by Metformin, the main drug used nowadays in the treatment of type 2 diabetes, in relation to the other antidiabetic therapies or the lack of treatment. This review aims to present and analyze some of the most recent published studies results about the relationship between type 2 diabetes mellitus and the incidence/mortality of several types of cancers, the carcinogenesis phenomena involved in this process, and the performance of metformin as a protective factor for the development of cancer in this population.

Keywords: Type 2 diabetes mellitus; Cancer; Metformin.
Resumo: Evidências epidemiológicas recentes apontam que o quadro de Diabetes mellitus tipo 2, tipo que representa 90% de todos diabéticos no mundo, está intimamente ligado ao aumento da incidência de determinados tipos de câncer, como pâncreas, mama, ovário, endométrio, fígado, cólon, estômago e pele, além de determinar evolução desfavorável nestes casos, aumentando a mortalidade dos pacientes acometidos simultaneamente por tais doenças, quando comparado a pacientes não-diabéticos que apresentam algum tipo de câncer. Estudos bem delineados demonstram, ainda, a existência de uma relação protetora, tanto para desenvolvimento quanto para progressão destes cânceres, proporcionada pela Metformina, principal droga utilizada no tratamento do diabetes tipo 2 atualmente, em relação a outras terapias antidiabéticas ou à ausência de tratamento. Esta revisão de literatura tem como objetivos apresentar e analisar resultados de alguns dos estudos mais recentes publicados acerca da relação entre Diabetes mellitus tipo 2 e a incidência/ mortalidade de diversos tipos de cânceres, os fenômenos de carcinogênese envolvidos neste processo, e a atuação da metformina como fator protetor do desenvolvimento de câncer nesta população.

Palavras-chave: Diabetes mellitus tipo 2; Câncer; Metformina.
INTRODUCTION

Diabetes Mellitus (DM) represents a heterogeneous set of organic dysfunctions that have as their central point the inefficiency in the maintenance of glycemic control due to the inability of synthesis or proper use of insulin.\textsuperscript{1,2}

This dysfunction is framed by the World Health Organization (WHO) in the group of chronic non-communicable diseases, which currently represents more than 70% of deaths around the world.\textsuperscript{1-3} In addition to the resulting impact of its severity, epidemiological studies indicate its significant global prevalence, affecting 9.2% of all men and 9.8% of women in the world in 2008. This repercussion led WHO to classify the DM as a worldwide epidemic.\textsuperscript{1-3}

Because of the wide variety of etiologies of diabetes, the American Diabetes Association (ADA) in 1997, divided its clinical presentation in four general subclasses, different from the classification previously adopted, based on the type of treatment. With this, the terms insulin dependant DM and non-insulin dependant DM became obsolete.\textsuperscript{4,5} The classification of ADA was reaffirmed and adopted in 2006 by the World Health Organization and recommended, from then on, by international guidelines, including the Brazilian Society of Diabetes, and maintained since then.\textsuperscript{6} The four general classes are: Type 1 diabetes mellitus (DM1), diabetes mellitus type 2 (DM2), other types of diabetes and gestational diabetes, as presented in table 1.\textsuperscript{1,2,4-6}

Table 1. Etiologic Classification of Diabetes Mellitus. Adapted from American Diabetes Association, 2009.\textsuperscript{9}

<table>
<thead>
<tr>
<th>I.</th>
<th>Diabetes type 1 (destruction of β cells, giving origin commonly to an absolute deficiency of insulin. 5 to 10% of all cases of diabetes)</th>
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<tbody>
<tr>
<td>a.</td>
<td>Of Immune Mediation</td>
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<td>b.</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>II.</td>
<td>Type 2 Diabetes (there can be from the predominance of insulin resistance associated with the relative deficiency of insulin, until a defect predominantly secretory of insulin with insulin resistance. 5 to 90% of all cases of diabetes)</td>
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<td>III.</td>
<td>Other specific types of diabetes</td>
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<table>
<thead>
<tr>
<th>a.</th>
<th>Genetic defects in function of β cells, characterized by mutations in:</th>
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<tr>
<td>1- Factor of nuclear transcription of hepatocytes (UH) 4α (MODY 1); 2- Glicoquinase (MODY 2); 3- HNF-1α (MODY 3); 4- Factor promoter of insulin 1 (IPF-1; MODY 4); 5- HNF-1β (MODY 5); 6- NeuroD1 (MODY 6); 7- mitochondrial DNA; 8- subunits of the potassium channel sensitive to ATP; 9- Proinsulin or insulin</td>
<td></td>
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<tr>
<td>b.</td>
<td>Genetic defects in insulin action</td>
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<td>1- insulin resistance type A; 2- Leprechaunism; 3- Syndrome of Rabson-Mendenhall; 4- lipodistrophic syndromes</td>
<td></td>
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<td>c.</td>
<td>Diseases of exocrine pancreas</td>
</tr>
<tr>
<td>Example: Pancreatitis, Pancreatectomy, neoplasia, cystic fibrosis, Hemochromatosis, fibrocalculous pancreatitis, mutations of the carboxyl ester lipase</td>
<td></td>
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<td>d.</td>
<td>Endocrine disease</td>
</tr>
<tr>
<td>Example: Acromegaly, Cushing syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, Somatostatin, aldosteroma</td>
<td></td>
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<td>e.</td>
<td>Induced by drugs of chemical substances</td>
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<td>Example: Glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid diazoxide, agonists β-adrenergic agonist, thiazides, Hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypical and others), epinephrine</td>
<td></td>
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DM2 is the most common form of disease, representing 90% of all DM cases. Of multifactorial origin, resulting from a complex interaction of genetic, immunological and environmental factors, its pathophysiology is based in dysfunction of insulin due to the emergence of resistance to its action, associated to a gradual secretory deficit of this hormone by pancreatic beta cells.\textsuperscript{1,2}

Once established, the DM progresses with involvement of intermediate metabolism, leading to hyperglycemia, which generates serious systemic repercussions such as neuropathy, diabetic retinopathy and nephropathy, in addition to significantly increasing the risk of vascular diseases and predisposing to acute ketoacidosis and hyperosmolar hyperglycemic state, of great morbidity and mortality.\textsuperscript{1,2} In addition to these clinical signs, the metabolic instability resulting from DM, associated to the effects on the endocrine and immune systems, is related to an increased risk of developing various types of cancers.\textsuperscript{7}

The relationship between DM and carcinogenesis is a very current point of discussion in the medical literature. In some well-designed studies a statistically significant increase was reported in the incidence or mortality of cancers of some organs, such as the pancreas, breast, ovary and endometrium, liver, colon, stomach and skin in diabetic patients. Other studies that followed a similar line of approach also indicated that metformin, an oral anti-diabetic of first line, currently considered the basis for the treatment of DM2, has been shown to be effective in the prevention of cancer and reduce mortality due to cancer among diabetic patients. However, in spite of the significant epidemiological impact of these studies, there is a need for further research to consolidate this relationship in the scientific literature.\textsuperscript{10,13-33}

This review aims to present and analyze some of the most recent published studies results about the relationship between type 2 diabetes mellitus and the incidence/mortality of several types of cancers, the carcinogenesis phenomena involved in this process, and the performance of metformin as a protective factor for the development of cancer in this population. .

**LITERATURE REVIEW**

DM, along with its complications, is considered the fifth leading cause of deaths, accounting for over 5% of all deaths each year, according to WHO estimates at the beginning of the 21st century.\textsuperscript{1-3}

To worsen the statistics, epidemiological studies point to a trend of increase of almost 100 million diabetics in the next 20 years, in relation to the current prevalence of approximately 387 million individuals affected.\textsuperscript{1} This increase is due to factors such as growth and population aging,
associated with obesity and a sedentary life style, which represents another major health problem worldwide, in addition to the increased survival of the diabetic patients themselves, with advances in monitoring and treatment of the disease.\textsuperscript{1,2}

In Brazil, data from the Ministry of Health reveal a growth of 61.8\% in the number of patients diagnosed with DM2 between 2006 and 2016. In 2006, the amount of Brazilians diabetics accounted for 6.9\% of the population, while in 2016, the statistics of this same body already pointed to a total of 8.9\%. Such data also revealed that the prevalence is lower among men (7.8\%) than among women (9.9\%).\textsuperscript{8} It is estimated that due to the chronicity of the disease and the severity of its complications, Brazil spends about 3.9 billion dollars per year with the management of diabetic patients. Therefore, DM represents a great impact not only for affected individuals and their families, but also for the health care system, bringing economic costs and intangible quality of life.\textsuperscript{1,2}

DM2, the most common type of disease, has as its pathophysiological basis the peripheral resistance to insulin action, which is related to several environmental factors and lifestyle that contribute effectively to its genesis. Among these factors the following stand out: obesity, a sedentary lifestyle and the diets rich in fat, typical of developed countries, countries which comprise 80\% of the global prevalence of this disease.\textsuperscript{1,2} In addition to the environmental factors, the genetic influence is without doubt a great impact, since the concordance between univitelline twins approaches 100\%. However, despite the clear association of genetic factors in the development of the disease, the heritability has not been fully elucidated, possibly due to its polygenic nature.\textsuperscript{1,2,9}

Just as the genetic influence, the mechanisms of carcinogenesis related to DM2 require further studies. It is known currently that both diseases share non-modifying risk factors (such as age, sex, race/ethnicity) and modifying ones (such as diet, physical activity, smoking, alcohol, obesity and weight change). In addition, some bodies of research suggest that cancer and diabetes can be triggered by similar molecular genetic mechanisms, as well as possess biological relationships (described below) that approach them even more.\textsuperscript{10}

The complex events that involve the carcinogenesis, obey certain steps that modify the physiological process of cell division and promote malignant transformation followed by tissue invasion and possible metastasis. These steps are represented by initiation (first step in irreversibility of cancer, from mutation of specific genes that regulate the cell cycle), promotion (stimulation of the growth of the cells affected) and progression (appearance of the most aggressive character of the promoted cells). The factors that interact synergistically with these steps may be associated with cancer incidence or mortality. The mechanisms by which diabetes may influence the neoplastic progression involve mainly the hyperinsulinemia (of endogenous cause, such as the mechanism to attempt to overcome the resistance provided in DM2, or exogenous, by means of treatment using insulin or other medicines that increase its synthesis or secretion), hyperglycemia or chronic inflammation.\textsuperscript{10}

The insulin, mean anabolic hormone in the metabolism of carbohydrates, exerts proliferative effects directly via the insulin receptor (IR), and indirect effects by increasing the circulating levels of insulin-like growth factor 1 (IGF-1). The insulin receptor is tyrosine-kinase type, similar to other growth factors and, as such, it has as a final result of delayed pathway of intracellular signals the activation of kinases with mitogen purpose, from the gene transcription.\textsuperscript{11} The majority of cancerous cells express this type of receptor on their surface.
Due to peripheral insulin resistance, the developing cancer cells receive more of this hormone and develop a phenomenon of up-regulation of the IRs. However, due to the fact that the cancerous cells have independent means of insulin for acquisition of glucose, the activity of insulin becomes less metabolic and more related to the mitotic capacity, leading to increasingly induction of kinase activating of mitotic and growth genes, thus increasing the multiplication and cell survival.\(^\text{10,12}\)

In turn, their indirect effect is through the reduction of hepatic production of protein 1 ligand of IGF, thus increasing the levels of IGF-1. This hormone, in addition to the anabolic effects related to an increase in blood glucose, protein synthesis and lipid degradation, has stimulating growth, increasing the rate of cell division and predisposing to the development of cancers.\(^\text{2,10-12}\)

The hypothesis that hyperglycemia (one of the main findings in diabetes mellitus) can have significant carcinogenic action, serving as a substrate for the process of carcinogenesis, emerged in the mid 1950s, since the studies of Otto Warburg. Normally, cancer cells produce ATP by anaerobic glycolysis. Under these conditions, the production of cytoplasmic ATP via glycolysis by tumor cells is less efficient than the synthesis via oxidative phosphorylation in mitochondria of normal cells. In addition to this mechanism, the high cellular activity, related to the proliferation induced by mutations, requires great synthesis activity of various products necessary for the progression. Cancer cells, therefore, need more glucose than normal cells, taking advantage of the hyperglycemia of Diabetes. Various types of cancers have been detected by positron-emission tomography based on this theory. In addition, the effects of high rates of glucose in stimulating the vasculogenesis and transformation were proved. However, hyperglycemia is considered by some authors as subordinate to the hyperinsulinemia as carcinogenic factor.\(^\text{10}\)

Whereas the chronic inflammation is related to central obesity, which is often associated to diabetes mellitus type 2 and can be a trigger for the carcinogenesis through pro-inflammatory cytokines secreted by adipose visceral tissues. These cytokines, such as adipokines, interleukin-6 (IL-6) and inhibitor of plasminogen activation 1 (PAI-1), are produced when there is excess of fat visceral compartment and give result to chronic inflammation of low degree in peripheral tissues, which provides an optimal microenvironment for tumor installation, with stimulus to blood supply to tumors, activation of transcription factors that increase the proliferation, survival and invasion, and inhibition of the immune pathways of tumor suppression.\(^\text{10}\)

The set of factors that relate the DM2 and the carcinogenesis are summarized in the following figure (Figure 1).

In spite of having possible common pathways of carcinogenesis, the strong association between cancer and diabetes depends on the type of cancer. The current studies reveal relation of statistically significant increase in the incidence or in aggressiveness of cancer of some organs such as breast, ovary and endometrium, pancreas, liver, colon, stomach and skin in diabetic patients.\(^\text{10,13-28}\)

The increase in risk of carcinogenesis for malignant tumors of the breast, ovary and endometrium in diabetic patients has the relationship between this disease and the increase of serum levels of estrogen. This hormone has an important function as a growth factor and has its primary synthesis in high peripheral fat due to metabolic disorders caused by DM, especially when it is associated with obesity.\(^\text{12,16}\)
The importance of this mechanism was also emphasized in studies that studied the relationship of gestational diabetes (GDM) as a triggering factor of cancer. A population study of case-control study carried out in Washington with an odds ratio of 1.73 and a confidence interval of 95%, showed that women with a history of GDM had a higher risk of developing cancer of the endometrium (EC) or endometrial hyperplasia (its predecessor), especially when these arise in women under 50 years of age and obese. Among the cases of HE/EC with a history of GDM, 40.4% had a diagnosis of DM2. Thus, it is estimated that as rates of obesity and type 2 diabetes mellitus increases in the United States and abroad, the rates of EC may also increase.17

Regarding breast cancer, other studies have confirmed not only the increase of its incidence, as well as its relationship with the increase of serum levels of estrogen triggered by DM2. A meta-analysis of 20 studies (5 case-control and 15 cohorts) developed in different countries in North America, Asia and Europe, with a relative risk of 1.20; with 95% of the confidence interval between 1.12 and 1.28, came to the conclusion that women with DM are 20% more likely to develop breast cancer. However, this association was not so well established when using population of women already in menopause stage, which strengthens the influence of estrogen levels in the pathogenesis of this type of cancer.15

As the cancer of the pancreas, in a meta-analysis showed that the likelihood of initial ealy DM2 to be a manifestation of pancreatic cancer, while the DM2 for long term development was considered a probable risk factor for this cancer. The high mortality for patients with cancer of

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Figure 1 - Physiological pathological relationship between Diabetes Mellitus type 2 and Cancer
the pancreas with DM2 is probably related to the aggressive growth of the tumor, which may be evidenced by markers of cancer as the CA19-9. Furthermore, the insulin therapy seems to reduce the incidence of cancer of the pancreas, probably reducing the blood glucose and thus reducing the supply of glucose to the tumor growth. Some studies state association of up to 70% of cancers with diabetes\textsuperscript{18-21}

Another study raised the association between DM and cystic pancreatic lesions (PCLs), an important precursor of cancers of the pancreas, especially when associated with obesity. Insulin resistance was considered as the central factor for the development of PCL, however, there is a need for further exploration to elucidate this association.\textsuperscript{22-24}

A cohort based on the population of Uppsala, Sweden, has confirmed the risk significantly increased of development of hepatocellular carcinoma, as well as cancer of the pancreas in diabetic patients, with a relative risk of 1.5. In the same way, in two large cohorts performed in Sweden and Denmark, and in one case-control study carried out in Italy, DM was listed as an independent risk factor for prevalence, recurrence and mortality for the hepatocellular carcinoma.\textsuperscript{13}

As for colorectal cancer, a dutch cross-sectional study carred out in a university hospital from the research of patients subjected to colonoscopy, concluded an increase from 20 to 40% in the risk of developing such cancer in diabetic patients compared to non-diabetics. In addition, It was detected higher presence of colorectal adenomas and serrated polyps (precursor lesions of cancer) in diabetic patients, compared to those who did not have the disease.\textsuperscript{25} Another study performed in Denmark noted further a statistically secure increase of 12% of mortality from colorectal cancer in diabetic patients.\textsuperscript{26}

In turn, it was observed in a meta-analysis of 22 cohort studies an important divergence between the relationship of risk and mortality of gastric cancer in diabetic patients compared to non-diabetics. Such contrast of results was interpreted by the authors as a factor that does not allow to relate such diseases, although in some of the cohorts used in the present study, in addition to other studies not included in this meta-analysis, such an association was made.\textsuperscript{27}

When it comes to skin cancer, a retrospective cohort study was performed involving the whole population of Taiwan, which obtained as results a relationship of significant increase in incidence of skin cancers, (including melanoma and non-melanoma) in diabetic patients compared to non-diabetic patients, with ratio of the incidence rates of 1.44 and P=0.02.\textsuperscript{28}

It is interesting to mention that not only the condition of full diabetes, but also the pre-diabetic state was associated with increased incidence of cancers. A meta-analysis of 16 studies of prospective cohort developed in different countries in North America, Asia, Europe and Africa, came to the conclusion that there is an increased risk of several types of cancer (mainly liver, endometrium and stomach/colorectal/) in pre-diabetic patients, with statistical significance (relative risk of 1.15; with 95% of the confidence interval between 1.06, 1.23). The authors of this study claim 15% increase in cancer risk among pre-diabetic patients, and of 22% in overweight diabetic patients.\textsuperscript{20}

Regarding the relationship between the use of metformin and better prognosis of cancer in diabetic patients, a recent meta-analysis of 19 studies involving 550,882 diabetic individuals suggested that the use of metformin reduced the
The proportion of liver cancer in 48% compared with those who did not use drug.29

The results of another meta-analysis showed that metformin exhibited greater protection for liver cancer compared with insulin, sulfonylureas and non-user of any diabetic medicine (MAD). Additionally, this study showed that the use of insulin increased the risk of liver cancer, possibly by its mitogen action. However, this assertion is subject to temporal bias, since insulin is more reserved for patients with diabetes of long duration or in more advanced stages, which may be associated with an increased risk of developing liver cancer.30 In line with this work, it was noticed in a Danish study a reduction of 15% of mortality related to colorectal cancer patients undergoing treatment with metformin, when compared with patients treated with insulin.26

Although the mechanism of action of metformin as protector for the development and progression of cancers is not still fully elucidated, it is possible to develop hypotheses based on their mechanism of action. Such mechanism comprises the blockade of gluconeogenesis (75% of its effect) and glycogenolysis and stimulation of hepatic gluconeogenesis. Added to this, there is the action of glucose control, with the sensibilization of the action of insulin, by encouraging the uptake of serum glucose by peripheral tissue-insulin-dependent diabetes from the increased activity of activated protein kinase by adenosine monophosphate (AMPK), a specific kinase that assists in regulating energy levels, leading to increased expression of molecules which catch glucose dependent insulin (GLUT4) in the cell membrane. In addition, due to not having a direct effect on the pancreatic release of insulin and by reducing the levels of blood glucose, this drug, indirectly, leads to reduced synthesis of pancreatic insulin and, consequently, of its circulating levels, avoiding the hyperinsulinemia and its mitogens effects.31,32

New studies also revealed that the activation of AMPK by this drug is capable of inhibiting cell proliferation, reducing the formation of colonies, causing a partial shutdown of the cell cycle in lineages of cancer cells or, at least in part, by inhibiting the synthesis of their proteins.10,31,32

The following figure summarizes the effects of metformin on its targets of action and the relationship with the reduction of tumor progression (Figure 2).

Figure 2 - Relationship between action mechanism of metformin and its effect on tumor progression.
Although this relationship between metformin and protection to cancer, according to what has been stated above, is logical, a possible bias that makes it difficult to calculate its real impact in epidemiological terms is the fact that the treatment of DM2 involves a dynamic process in which the MADs can be exchanged continuously and associated with other medications. This creates great difficulty in the analysis of the benefits of the use of metformin as monotherapy or the effects of synergism or antagonism in protecting against cancer when this drug is used in combination with other MADs.

**CONCLUSION**

Diabetes and cancer are complex diseases and of great repercussion on public health worldwide, implying a great impact on the quality of life of the people affected by these diseases. The association between them is based on the principle that they share many risk factors and pathophysiological relationships. In addition, the scientific bodies of research show that both metabolic and hormonal background of DM2 including hyperglycemia, hyperinsulinemia, changes in estrogen levels and deregulation of pro-inflammatory cytokines, can increase the risk of developing or progression of cancer. On the other hand, when one takes into account the treatment of diabetes, studies suggest that therapy with metformin has likely protective effect for cancer at the expense of results obtained with other therapies, such as the exogenous insulin. However, even with the construction of positive evidence that strengthen and possibly confirm such assumptions in most exploratory analyzes, a cautious interpretation is necessary, since there is still a need to compare and repeat the results obtained in the present study, in addition to eliminating some biases of research that impede the consolidation of factual relationship between the two diseases, including the effects of the treatment of each other. It is believed that once well elucidated such points, it will be possible to use metformin as a drug associated with the treatment of cancer in diabetic patients, as a protective factor in the progression of both diseases for unfavorable outcomes.

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**REFERENCES**


19. LI, D. *et al.* Antidiabetic therapies affect risk of


