Medical and Research Publications
International Open Access

Review Article **Journal of MAR Oncology (Volume 4 Issue 6)**

Metformin and Cancer: Genetic Changes with the Use of Metformin in Patients with Head and Neck Tumors. Is there a Role for this Old Drug?

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Received Date: November 11, 2022

Published Date: December 01, 2022

Abstract

There is increasing evidence that metabolic reprogramming promotes a cell's ability to proliferate rapidly, even under stressful conditions ***[****1,2****]*** *This has sparked some interest in investigating the action of new agents that target these metabolic abnormalities in cancer patients, especially the study of metformin and its antitumor effects, as it is a drug with high levels of safety and low cost.*

In addition to its antidiabetic properties, metformin has been shown in numerous studies to possess anticancer activity, which has attracted increasing attention. It has been shown to inhibit cell proliferation in several types of human malignancies, including gastric cancer, pancreatic cancer, medullary thyroid cancer, breast cancer, and head and neck carcinoma, among others. ***[****3****]****. It is for this and other mechanisms that we will described in this review that it is biologically plausible that metformin is postulated as a drug with antitumor action in patients with head and neck cancer.*

Why head and neck tumors? *Epidemiologically speaking, it is a common pathology in various regions of the world. Each year more than 550,000 cases are diagnosed worldwide.* ***[****4****]*** *Treating patients with head and neck tumors is a highly complex task. These type of tumors have a significant impact on the patient's quality of life, by affecting basic functions such as chewing, swallowing, breathing; alter the senses of taste, hearing and smell, as well as human characteristics such as appearance and speech. Therein lies the importance of studying this pathology as well as identifying new, less toxic treatments. The objective of the review will be to analyze the genetic alterations in head and neck tumors with the use of metformin, taking into account 5 study genes (AMPK, pAPMK, mTOR, PI3K-AKT, LKB1).*

The Methodology that will be carried out to fulfill this objective is a bibliographic review to obtain results related to the relationship between the use of metformin and the genetic changes that it produces in head and neck tumors, the bibliography available to date will be selected in which content topics related to the topic are addressed.

Key Words: *mouth cancer, laryngeal cancer, head and neck cancer, squamous cell carcinoma, squamous cell carcinoma, metformin, AMP-activated protein kinases, apoptosis.*

Introduction

Cancer is a global disease that represents a major public health problem, the GLOBOCAN 2020 data reports that 19,292,789 new cases were diagnosed and 9,958,133 died, these incidence data show an increase in cases compared to past years, this is due to numerous changes in lifestyle, increased sedentary lifestyle, smoking, alcohol consumption, HPV **[**4**]** infection; as well as chronic diseases, including diabetes mellitus, especially type 2 (DM2).

Over the last few years, numerous studies have observed that people with DM2 have a higher risk of being diagnosed with a neoplasm throughout life and that they have a disease with a worse prognosis, those patients who receive metformin as treatment experience a lower incidence and mortality from cancer**[**5**]**. These studies, including basic, epidemiological, preclinical and clinical studies, have found different antineoplastic mechanisms with the use of metformin, including insulin sensitizing mechanisms and antiapoptotic mechanisms that give the cell the ability to alter cell function. of the tumor cell leading to its death.

Diabetes mellitus is currently a true global epidemic. According to the World Health Organization (WHO), today there are about 200 million people with diabetes. This figure could double in the next 10 years. **[**6**]** It is logical to think that a significant percentage of these patients will develop some type of cancer, several investigations, among which are those of Marble dating back to 1936, have described the relationship between DM 2 and cancer, where there is not only an increased risk of cancer, but in them mortality is higher, The strength of association is 1.2 to 4 times. **[**7**]**

In recent years, there has been some interest in investigating the action of new agents that target metabolic abnormalities caused by carcinogenesis. A number of specific genetic, epigenetic events and patterns of gene expression have been identified; the genetic changes and gene expression patterns that drive the neoplastic process contribute to a model of molecular progression.

Head and neck cancer (HNSCC) refers to malignant tumors of the upper aerodigestive airway, from the lip to the larynx, as well as those derived from the salivary glands and paranasal sinuses. Major risk factors associated with head and neck cancer include tobacco use, alcohol use, human papillomavirus (HPV) infection, and Epstein-Barr virus (EBV) infection. **[**4**]** The relative prevalence of these risk factors contributes to variations in the observed distribution of head and neck cancer in different areas of the world. Chronic exposure of the upper digestive tract to these and other risk factors produces so-called "field carcinogenesis", a process in which patients with cancer or premalignant dysplastic lesions in the

oropharyngeal mucosa are at significant risk for this type of cancer. **[**8**]**. There are also risk factors through multiple genetic pathways that may contribute to an increased risk of head and neck cancer by interacting with other risk factors listed. These include metabolic polymorphisms that influence exposure to carcinogens in tobacco smoke, DNA repair gene polymorphisms, as well as variations in other pathways that contribute to carcinogenesis.**[**8**]**

Epidemiologically speaking, it is a common pathology in various regions of the world. Each year more than 550,000 cases are diagnosed worldwide. Males are more affected than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males is greater than 20 per 100,000 in the regions of France, Hong Kong, the Indian subcontinent, Central and Eastern Europe, Spain, Italy, Brazil, and among African Americans in the United States.

The present work describes the genetic alterations of the use of metformin in patients with head and neck tumors from the changes at the genetic level in head and neck tumors with the use of metformin, taking into account 5 genes , AMPK, pAPMK, mTOR, PI3K-AKT, LKB1 due to the inhibitory activity of metformin on these pathways already described in breast tumors previously.

Objectives

The objective of the review will be to analyze the genetic changes in head and neck tumors with the use of metformin, taking into account 5 genes (AMPK, pAPMK, mTOR, PI3K-AK, LKB1).

Methodology

A systematic bibliographic review was carried out to review different scientific papers: Cochrane Library, Embase, LILACS, MEDLINE and PubMed databases. Works performed in vitro and in vivo were included in the review. All selected studies were methodically assessed according to the Recommendation Rating Assessment, Method of development and evaluation to make a judgment of the quality of the evidence.

Antineoplastic Effects of Metformin

Metformin is a synthetic biguanide that was discovered in the 1920s as a byproduct of N-dimethylguanidine synthesis. As a first-line drug in the treatment of type 2 DM, metformin has become widely used around the world. **[**3**]**

The main mechanism of action of metformin is metabolic, by inducing energy wear on cells (adipocytes, neoplastic cells), forcing them to activate metabolic pathways and, if this is not achieved, induce apoptosis mechanisms through mitochondrial toxicity. The drug accumulates in the mitochondrial matrix and achieves complex I inhibition of the respiratory chain; this effect generates a reduction in NADH oxidation and finally, a decrease in cellular concentrations of ATP, with the consequent activation of AMPK.**[**3**]**

Recent studies show that the action for the inhibition of gluconeogenesis occurs in the mitochondria. Metformin inhibits the mitochondrial isoform of the enzyme glycerol phosphate dehydrogenase, an enzyme that catalyzes the conversion of glycerol phosphate to dihydroxyacetone phosphate, this decreases the concentration of Nicotin Adenine Dinucleotide (NAD) in the cytosol and, therefore, increases the nicotin adenine dinucleotide ratio reduced (NADH)/NAD in this compartment and secondarily decreases this ratio in the mitochondria, which in turn restricts the conversion of lactate to pyruvate, thus preventing the use of these substrates for gluconeogenesis. In this way, hepatic glucose production decreases and excess glycerol and lactate are released into the plasma.**[**3**]**

Historical data indicates that in the 1970s, Vladimir Dilman and Anisimov proposed the hypothesis that biguanides had protective antiaging and anticancer effects through "metabolic rehabilitation", and later suggested that they also had chemopreventive and synergistic activity, with chemotherapeutic agents such as cyclophosphamide .**[**9**]**

They demonstrated the antineoplastic effects of metformin in laboratory animals, in transgenic mouse models of breast cancer that overexpressed Her2/neu. **[**9**]**

In 2006, Zakikhani et al. described the antineoplastic effect of metformin on breast tumors through the activation of liver kinase B1 (LKB1) and its target protein, cyclic adenosine monophosphate-dependent kinase. (AMPK), involved in the control of hyperglycemia **[**10**]**. Later, he reported that it induced cell cycle arrest, produced a reduction in the accumulation of p53 existing in some states, such as obesity and hepatic steatosis, by reducing the signaling of growth factors, and inhibiting oxidative phosphorylation in

mitochondria [1], this effect is achieved by blocking complex I of the electron transport chain, which leads to apoptosis.

On the other hand, recent research has described different mechanisms of action of metformin on the immune system, also exerting antitumor effects through this pathway [9], in addition to blocking a variety of transcription factors (called Yamanaka factors: OCT4, KLF4 , SOX2, cMyc), as well as the action of essential microRNAs for the transcription of factors such as FOXO or CREB.

Effects on Metabolism

The Warburg effect

Neoplastic cells carry out metabolic reprogramming, this to increase the production of nucleotides, amino acids and lipids. The result is a set of metabolic changes to tumor biomass, in order to guarantee cell proliferation; to achieve this, the neoplastic cell induces changes in the pathways for obtaining ATP, switching from oxidative phosphorylation to aerobic glycolysis (Warburg effect).[11]

Aerobic glycolysis is an inefficient way to generate adenosine 5′-triphosphate (ATP). It has been shown that the metabolism of the neoplastic cell is adapted to facilitate the uptake and incorporation of nutrients into the biomass (eg, nucleotides, amino acids, and lipids) necessary to produce a new cell. To achieve this, several signaling pathways are involved, which are altered by mutations characteristic of the neoplastic cell, allowing it to metabolize nutrients in a manner conducive to cell proliferation, instead of an efficient production of ATP[11].

The Warburg effect maintains that what leads to carcinogenesis is defective cellular respiration caused by damage to the mitochondria, and also describes that cancer cells make use of glycolysis followed by lactic acid fermentation as a source of energy, even if there is oxygen in sufficient quantity. suitable for breathing.

This raises the next question, why the neoplastic cell uses a less efficient metabolism, at least in terms of ATP production?

One possible explanation is that inefficient ATP production is a problem only when resources are scarce. This is not the case for neoplastic cells which are constantly proliferating as they constantly receive a continual supply of glucose and other nutrients from the bloodstream. [eleven]

The effect is initiated by the activity of adenylate kinases that buffer the decline in ATP production by converting two ADPs to one ATP and one AMP (adenosine 5′-monophosphate). This helps maintain a viable ATP/ADP ratio as ATP production decreases, but the accumulation of AMP activates AMP-activated protein kinase (AMPK).

This activation depends on the tumor suppressor protein LKB1 and leads to the phosphorylation of various targets to improve the energy charge in cells. **[**10**]**

A second possible explanation for the switch to aerobic glycolysis is that neoplastic cells have important metabolic requirements that extend beyond ATP.

For example, in neoplastic cells that depend on aberrant signals in the PI3K/AKT/mTOR pathway, activation of PI3K causes an increased dependence on glycolysis and uses metabolites from glycolysis to synthesize non-essential amino acid, nucleotide, and fatty acid intermediates, which are essential for cell proliferation. From what has been described, it is not absurd that the cancer cell activates pathways that do not produce much ATP in the presence of oxygen, becoming a cell "addicted" to glucose. **[**11**]**

Embryonic cells use similar processes for their proliferation, and the neoplastic cell exhibits phenotypic features of stem cells.

However, not all tumors or all cells of the same cancer adopt a metabolic reprogramming according to the Warburg effect. Instead, they exhibit an opposite mitochondrial respiratory-type phenotype, with increased oxidative phosphorylation at this level. In this case, the inhibitory effect of metformin on complex I is beneficial, since it interferes with the metabolism of the neoplastic cell. **[**11**]** There are tumors where there is a metabolic synergism between normal and tumor stromal cells. In this sense, tumor-associated fibroblasts are glycolytic, and provide lactate and amino acids to oxidative tumor cells that will be used as a source of energy thanks to their high mitochondrial metabolism, or they can incorporate them as metabolic precursors, necessary for tumor development. It is important to understand this characteristic of the tumor cell since metformin plays a dual role, on the one hand it uncouples oxidative phosphorylation by blocking complex I, and on the other hand it inhibits hexokinase 2 (regulates the glycolytic pathway) leading to apoptosis cell phone. **[**12**]**

Inhibition of Ampk-Dependent Growth

The increased activity of the AMPK signaling pathway plays an important role in the cellular energy balance and it's mediator of almost all the actions of the drug at that level. The increase in AMPk activity inhibits a complex of enzymes (mTOR), which participate in the signaling pathways for the synthesis of different growth factors, and cellular energy balance. **[**13**]**The action of metformin and exercise on AMPK requires a well-known tumor inhibitor called LKB-1, which has been identified in multiple epithelial-type neoplasms (breast, lung, melanoma, head and neck cancer) **[**10**]**. LKB1 was previously described as a tumor suppressor gene, whose loss of function is associated with Peutz-Jeghers syndrome. The molecular mechanisms of action of LKB1 include regulation of gluconeogenesis in hepatocytes and more generally as a tumor suppressor gene in epithelial tissues, thought to be involved as an activator of AMP kinase.**[**13**]**

It is important to note that part of the action of metformin requires adequate LKB1 expression, so the lkB1 gene polymorphism could be a predictor of response to metformin. **[**10**]** What is presumed is that metformin, by upregulating AMPK, would inhibit mTOR activation and therefore subsequent events in the signaling pathway; it interferes with mitosis by repressing various genes involved, such as tubulins, kinekines, histones, etc.**[**10**]** On the other hand, it leads to the activation of p53 by phosphorylation, and stops cell senescence because it interferes with the metabolic reprogramming carried out by the neoplastic cell for its survival **[**1**]**. It contributes to maintaining cell polarization and adhesion (capacity that is lost in cancer cells), and finally induces mitochondrial biogenesis. **[**12**]**

Mahvash Zakikhani et al, showed that the activation of the AMPK pathway by metformin is not limited to hepatocytes, but can also be observed in epithelial cells where there is a reduction in proliferation and a reduction in protein synthesis as a result of blocking the activation of the mTOR pathway. **[**13**]**

There is currently evidence that metformin can effectively suppress tumor growth by LKB1-independent mechanisms.

The antiproliferative actions of metformin where the AMPK pathway is activated are consistent with AMPK's role as an energy sensor that regulates processes, such as protein synthesis, when more energy is needed. Thus, by pharmacologically activating some of the intracellular control systems physiologically activated by nutrient deprivation, metformin acts as a proliferation inhibitor. **[**10**]**

Mechanism of Action of Metformin on the mtor Pathway

mTOR is a subunit common to two multiprotein complexes, mTORC1 and mTORC2. AMPK activation constitutes an inhibition pathway of the mTORC1 group, fundamentally through the phosphorylation and stabilization of tuberous sclerosis complex 2 (TCS2), which is a tumor suppressor.

Under normal conditions mTOR is responsible for controlling metabolism and cell growth signals, this is done through the activation of a signaling cascade that induces cell anabolism, protein synthesis, growth, survival, cell proliferation and inhibition of autophagy **[**10**]** Metformin blocks this activity, making mTOR unresponsive to signals from growth factors and nutrients. This has an effect on tumor and vasculature shrinkage **[**14**]**

The result of the activation of AMPK signaling by metformin, consequently reduces the activity of mTOR in its mTROC1 complex. This makes it an attractive drug to prevent and treat tumors in which the mTOR pathway is involved, as is the case with head and neck tumors. This has been demonstrated in in vitro and in vivo studies. **[**15**]**

It has also been shown that metformin inhibits mTOR activity through AMPK-independent pathways by inhibiting IGF-1, the insulin receptor, and AKT (or PKB). By this route, biguanide also reduces insulin and IGF-1, and reinforces the antitumor effect. **[**14**]**

Effect of Metformin on Head and Neck Tumors

Why head and neck tumors?

Head and neck cancer refers to malignant tumors of the upper aerodigestive airway, from the lip to the larynx, as well as those derived from the salivary glands and paranasal sinuses. Regarding the treatment of these tumors, the results continue to be, in many cases, poor.

For example, for tumors of the larynx, hypopharynx, and nasopharynx; treatment may consist of primary surgery, radiation therapy, or chemoradiation therapy **[**16**]**. Surgical treatment can have high morbidity, and chemoradiotherapy toxicities are common and can negatively impact patients' quality of life.

Major risk factors associated with head and neck cancer include tobacco use, alcohol use, human papillomavirus (HPV) infection, and Epstein-Barr virus (EBV) infection. Chronic exposure of the upper digestive tract to these and other risk factors produces the so-called “field carcinogenesis”, a process in

which patients with cancer or premalignant dysplastic lesions in the oropharyngeal mucosa are at significant risk for this type of cancer. [17]

There are also risk factors through multiple genetic pathways that may contribute to an increased risk of head and neck tumors, by interacting with other risk factors mentioned. These include metabolic polymorphisms that influence exposure to carcinogens in tobacco smoke, DNA repair gene polymorphisms, as well as variations in other pathways that contribute to carcinogenesis.

Epidemiologically speaking, it is a common pathology in several regions of the planet. Each year more than 550,000 cases are diagnosed worldwide. Tumors of the oropharynx and larynx are particularly common in East Asia, parts of Eastern Europe, and South America. [18] In Bolivia it occupies the first places in incidence and mortality, determining great disability and morbidity, for which they deserve special treatment.

Genetic and epigenetic changes

Carcinogenesis in HNSCC is driven by various signaling pathways, including[19]: Epidermal growth factor receptor (EGFR)

- p53
- p16,
- Insulin growth factor (IGF) receptor
- Cyclin D1
- Human papillomavirus (HPV)/E6/E7
- Phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway
- Nuclear factor kappa B and hypoxia-inducible factor 1 alpha.

Associations between signaling pathways and metabolism have been extensively studied in various tumor types; however, little is known about the carcinogenesis of HNSCC.

The identification of genetic changes and gene expression patterns responsible for the neoplastic process contribute to a model of molecular progression for this type of neoplasia. The systematic review by Daniela Fortunato Rêgo et al in 2016, makes a detailed description on moderate increases in the number of EGFR copies, participation in other parallel signaling pathways through other receptor tyrosine kinases

or G proteins can increase the effects of EGFR and produce effective blockade with EGFR antibodies or inhibitory small molecules used for treatment. [19]

Eukaryotic initiation factor protein (eIF4E) binds to messenger RNA during protein synthesis, and its overexpression can lead to upregulation of proteins essential for cell growth and division. This event has been found in head and neck tumors, and could be related to neoplastic transformation.

Cell cycle and apoptosis

Several studies have shown that the accumulation of cells in the G0/G1 phase after treatment with metformin produces a metformin-dependent enhancement in the apoptotic activity of other treatments such as dasatinib in Ca9-22 HSC3 cells.[20,21]. Metformin increases the proportion of cells in the G0/G1 phase in three cell lines in head and neck tumors (CAL27, WSU-HN6, and in SCC25 cells). Furthermore, it induces a significant increase in the proportion of apoptotic tumor cells 48 h after treatment in CAL27, WSU-HN6 and SCC25 cells.

Protein expression level regulation: The work of Lin et al[21] demonstrated metformin-dependent enhanced effects of dasatinib on AMPK phosphorylation and elongation factor 2, in addition to downregulation of EGFR, in sensitive HSC3 tumor cells. This work confirmed the role of metformin in the expression of cell cycle regulatory proteins (AMPK, mTOR, S6 kinase, cyclin D1, retinoblastoma protein, CDK 4 and 6, p21 and p27) in squamous cell carcinoma. This effect on the expression of cyclins and CDK inhibitors in HNSCC, at 24 and 48 h after treatment, produces a dose-dependent decrease in the expression levels of cyclins D1 and E in FaDu and D562 cell lines. [20].

The uptake transporter OCT3 plays a key role in mediating the intracellular effects of metformin on AMPK activation and subsequent inhibition of mTORC1 activity. In combination with 2-DG, metformin triggers AMPK phosphorylation. that does not occur if metformin is given alone.[22]

Vitale-Cross et al [23] found that, in the absence of AMPK activation, metformin treatment leads to a decrease in mTORC1 and thus in malignant cell proliferation. In xerograft models, there is a reduction in the levels of phosphorylated S6 after metformin treatment, while the unphosphorylated fraction of 4E-bound protein 1 (4E-BP1) increases, leading to a cumulative decrease in 4E-BP1 . [15] Consistent with its known activities, metformin treatment resulted in increased levels of phosphorylated AMPK, while both treatments reduced phosphorylated S6.[15]

Therefore, metformin regulates the activity of the mTOR signaling pathway in head and neck tumors, in in vitro models. Likewise, the reduction of OCT3 reduces the effect of metformin on cell proliferation in vitro and its antitumor effect in vivo. [22]

Metformin causes an increase in the expression levels of activated caspase-3, as well as an initial upregulation followed by a downregulation of the expression of 78 kDa glucose-regulated proteins in KB cells.

Inhibitory effects of metformin in vitro

In order to arrive at the dose of metformin relevant in the clinical scenario, a series of in vitro studies were first performed, where the concentrations of metformin in the plasma of mice using different doses were explored. In the work of Dmitri Madera et al. [15] 2.5 mg/mL of metformin in drinking water resulted in approximately 2 mg/mL of metformin in plasma, which is within the concentration found in humans treated with this drug. They achieved this by transplanting three oral mucosal squamous cell carcinoma cell lines (CAL27, CAL33, and UMSCC47) into recipient mice, and distributed between control mice and metformin-treated mice. They found that a dramatic decrease in tumor progression occurs in all HNSCC xenografts. Tumor reduction was seen in all those treated with metformin. There was no difference in the body weight of the mice that were treated with metformin vs. the control group.

In the study by Qingqiong Luo et al [24] BALB/c nude mice (male, 4 weeks old) were purchased from the Shanghai Laboratory Animal Center. Mice were also transplanted with three oral mucosal epidermoid tumor cell lines (CAL27, WSU-HN6). Cells were treated with or without 20 mM metformin for 24 hrs and 48 hrs. The study showed that the drug inhibits the proliferation of oral mucosal tumor cells and reduces colony formation in vitro. An inhibition was produced in the three cell lines by metformin in a dependent manner of exposure time to metformin (24, 48 and 72hrs) and dose. The proportion of cells in S phase decreased, while there was no significant change in the number of cells in G2/M phase. The most notable changes were loss of cyclin D1, increased p-AMPKα levels in metformin-treated cells indicated activation of the AMPK pathway. Protein levels of p-mTOR, p-S6K, and p-pRb also decreased dramatically in response to metformin treatment.

The G0/G1 transition revealed an obvious decrease in CDK4 and CDK6 levels in OSCC cells treated with metformin. However, no significant changes in the expressions of p21 and p27 were detected. These results clearly demonstrate that metformin affects the expression and phosphorylation of key cell cycle

regulatory proteins leading to G0/G1 arrest in human OSCC cells.[24] The results of this study demonstrated that oral administration of metformin led to a substantial inhibition of tumor growth by 58.77%.

Inhibitory effects of metformin in vivo

Qingqiong Luo et al [24] further investigated the in vivo effects of metformin on buccal mucosa squamous cell carcinoma cell lines, once the mouse had developed and palpable tumor, the mice were randomly assigned into groups control and treated. Metformin was administered orally to the treated group diluted in water (200 μg/ml), while control mice received only water. To assess the effect of the drug, the size and weight of the tumor were measured. Metformin-treated nude mice had a significant reduction in tumor burden compared to control mice. Metformin markedly reduced cyclin D1 expression and increased the number of apoptotic tumor cells.

Does metformin have a survival benefit in patients with head and neck tumors?

In the study by Alexandra E. Quimby [16], which included 1,679 patients with tumors of the nasopharynx, hypopharynx, or larynx, in whom metformin was administered from diagnosis and divided into groups that received metformin concomitant to treatment designated by the investigator for 1 year, 4 months and 1 month from his diagnosis. Patients were classified into one of six groups: 1) primary surgery with or without adjuvant radiation and/or chemotherapy, 2) primary radiation therapy with or without adjuvant/salvage surgery, 3) chemoradiation therapy with or without adjuvant/salvage surgery, 4) induction chemotherapy, 5) palliative/no treatment, or 6) other types of therapies not included in those mentioned. The results of the study showed no benefit in survival with the use of metformin in squamous cell cancer of the larynx, nasopharynx or hypopharynx.

Sandulache et al. [25] conducted a large retrospective cohort study to examine the association between metformin use and improved survival in patients with laryngeal tumors. In multivariate analysis, they showed an improved median survival ($p = 0.04$) when comparing diabetics who used metformin with diabetics who did not take it. However, they did not show an improvement in overall survival or statistical progression-free survival.

Discussion

Most cases of head and neck tumors arise in the oral cavity and continue to be a major public health problem. Despite the use of multiple treatments, the prognosis remains poor. Treating patients with head and neck tumors is a highly complex task. These types of tumors have a significant impact on the patient's quality of life, by affecting basic functions such as chewing, swallowing, breathing; alter the senses of taste, hearing and smell, as well as human characteristics such as appearance and speech. **[**18**]** There lies the importance of studying this pathology, and understanding the activation pathways of carcinogenesis, cell proliferation, tumor progression and resistance to different treatments at the molecular level, in order to develop new treatments that are more effective, less toxic and easy access.

Metformin is a biguanide that has been used for its insulin-sensitizing and glucose-lowering effects in type 2 diabetes mellitus. It has been shown to have antineoplastic activity in vitro and in vivo **[**24**]**. Numerous studies have shown the antitumor effect of metformin on cancer progression, as we have described in this review. Therefore, metformin, an old and widely used drug around the world, is gaining more and more attention as an anticancer agent.

The mechanisms underlying the possible anticancer effect of metformin have not yet been fully elucidated. Data from preclinical and preclinical studies suggest that metformin's amelioration of insulin resistance/hyperinsulinaemia and glucose lowering may play a role, however, there is growing evidence of direct effects of metformin on cancer cells, and promising models have been proposed suggesting inhibition of cell proliferation and cancer progression, cell cycle arrest, and stimulation of apoptosis **[**20**]**. Regulation of the cyclin D1 pathway in response to metformin has been demonstrated in various cancer cell lines including head and neck tumors. The detection that occurs in the G0/G1 phase of the cell cycle has been correlated with a marked decrease in the expression of cyclin D1 and phosphorylation of pRb, two important regulators of the cell cycle. Therefore, cyclin D1 could be a potential target for the treatment of these patients. **[**26**]**

The combination of metformin with other drugs inhibits the proliferation of cancer cells**[**23**]**. Multiple genetic changes that lead to cancer progression cause dysregulation of the G1 to S transition in the cell cycle. Several authors have shown the accumulation of cells in the G0/G1 phase when head and neck tumor cell lines were treated with metformin. AMPK activation and subsequent inhibition of mTORC1 signaling, reduction of cyclin D1 levels, and AKT dephosphorylation (at Ser473) participate in the apoptotic process induced by metformin**[**13**]**.

It is becoming increasingly clear that phase 3 trials must incorporate the study at the molecular level of the different tumors to understand the metabolic pathways involved in carcinogenesis and thus be able to incorporate drugs with activity on it, particularly with regard to the use of metformin. Preclinical trials already describe that the improvement of insulin resistance/hyperinsulinaemia and glucose lowering by metformin may play a role, both in the insulin-IGF1 system and in hyperglycaemia. It is of particular interest to include in randomized clinical trials the study of the effect of metformin on the regulation of the PI3K/AKT/mTOR signaling pathway, which is of utmost importance in carcinogenesis. Previous studies have reported that mTOR plays a key role in the control of cell growth, proliferation, and metabolism, and mediates the PI3K/AKT signaling pathway, which is frequently dysregulated in human cancers. **[**19**]**

Multiple genetic changes leading to cancer progression in head and neck tumors cause dysregulation of the G1 to S transition. The G1 phase of the cell cycle is controlled by a dynamic interaction between cyclins D1 and E, CDK 2 , 4 and 6 and the CDKIs, including members of the CDK-interacting protein/kinase inhibitory protein (Kip) and CDK4 inhibitors. During the transition from G1 phase, Kip1/p27 levels decrease to allow the cyclin/CDK complex to initiate transcription of genes required for G1-S progression. Activation of AMPK and subsequent inhibition of mTORC1 signaling, reduction of cyclin D1 levels, and dephosphorylation of AKT (at Ser4 73) participate in the apoptotic process induced by metformin. **[**24**]** The effects of metformin on the catalytic subunits of cyclin D1, CDK4, and CDK6 in squamous cell carcinoma of head and neck tumors remain unknown. **[**24**]**

Therefore, cyclin D1 is a potential molecular target for the treatment of these tumors. In addition to its effect on cyclin D1, metformin strongly inhibits pRb phosphorylation in head and neck tumors by blocking E2F activation. Increased expression of E2F is associated with malignant transformation, and down regulation of E2F is associated with induction of apoptosis and cell cycle arrest. This suggests that metformin could be developed as a potential therapeutic agent to block tumor progression in patients with head and neck tumors. **[**24**]**

This review suggests that metformin could be developed as a potential therapeutic agent in head and neck tumors, especially in combination with other agents, based on studies analyzed in vitro and in vivo in head and neck tumors, and based on the data of the antineoplastic effect in other tumors described in reviews and preclinical trials, such as breast cancer (especially the HER2 subtype), prostate and non-small cell lung cancer. **[**27**] [**28**] [**14**]**

Although supported by convincing basic and preclinical evidence of antitumor activity of the drug, clinical trials with data on survival are contradictory, therefore more studies with large sample sizes and designed to study genetic changes at the molecular level of the drug on the tumor are needed. tumor, this, to investigate the relationship between metformin and the survival of patients with head and neck cancer in its different stages, being a pathology of high incidence and to have solid evidence data and to be able to incorporate it into our usual clinical practice .

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