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REVIEW ARTICLE

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The impact of metformin on the development and course of anaplastic thyroid cancer in comparison to other histologic types of thyroid cancer

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ABSTRACT

Anaplastic thyroid cancer (ATC) is the rarest (1–2%) form of thyroid cancer, but also the most aggressive and associated with the worst prognosis. The survival median rate is 5–6 months, whereas only 20% of patients survive more than one year from the diagnosis, even though the usage of radiotherapy and surgical resection. The growing incidence rate of thyroid cancer and ATC determine the need for new prophylactic, diagnostic and therapeutic solutions.

Metformin was first introduced as an oral antidiabetic drug. The beneficial effect of metformin on anaplastic thyroid cancer cells was confirmed, however, the mechanism of this interaction is still unclear. The usage of metformin in thyroid cancer prevention is still under discussion — nevertheless, studies conducted on larger groups support this beneficial impact, at least in patients with insulin resistance or metabolic syndrome. Both the synergistic effect of metformin in anaplastic thyroid cancer chemotherapy and its protective effect in radiotherapy are still concerns and need additional confirmation in randomized clinical trials.

This review aims to sum up the recent knowledge on metformin usage in ATC.

Keywords: metformin, anaplastic thyroid cancer, anaplastic thyroid carcinoma, thyroid cancer, oncology, endocrinology, endocrine oncology

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Introduction

Thyroid cancer is the most common endocrine tumour, even despite its geographical disparity [1]. It occurs more often among women over 40 years of age. The main thyroid cancer diagnostic methods are ultrasonography and fine needle aspiration biopsy, which allow to describe the size, localization and histological subtype of the lesion. First-line treatment method in thyroid cancer is surgical thyroidectomy, usually with regional lymph nodes inclusion. In selected situations (especially in anaplastic thyroid cancer) radiotherapy is also used. Immunological therapy is also considered in anaplastic thyroid cancer (ATC) due to its high severity and effectiveness confirmed in recent studies [2–4].

Anaplastic thyroid cancer is the rarest (1–2%) type of thyroid cancer, but also the most aggressive and associated with the worst prognosis. The survival median rate is 5–6 months, whereas only 20% of patients survive more than one year from the diagnosis, even though the usage of radiotherapy and surgical resection [5]. The growing incidence rate of thyroid cancer, and ATC in particular, determines the need for new prophylactic, diagnostic and therapeutic solutions [6].

Metformin, chemically one of the biguanides, was first synthesized in 1920, and since the 1950s it is widely used as an oral antidiabetic drug as a first-line treatment in type 2 diabetes (T2D). Metformin dissemination among patients and physicians let this drug to show its non-diabetic therapeutic effects, like lowering the risk of fatty liver disease or improving body mass loss among the obese [7].

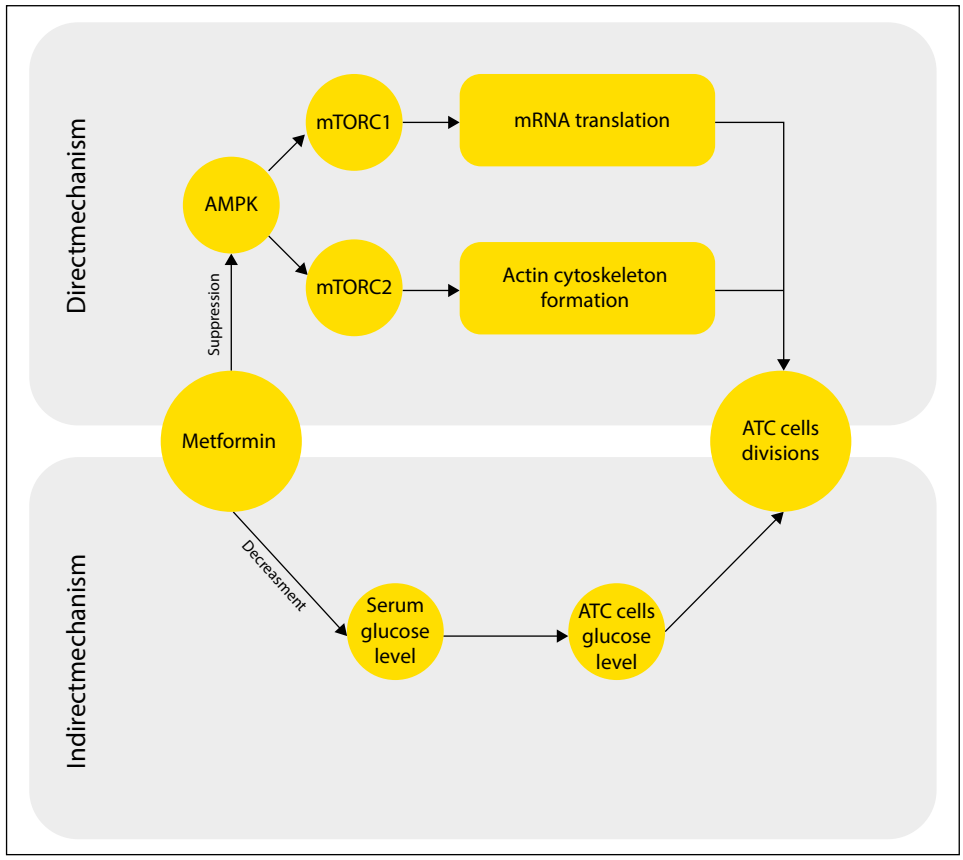

Figure 1. Diagram of potential suppressive effects of metformin on ATC proliferation; AMPK — adenosine monophosphate-activated protein kinase; ATC — anaplastic thyroid cancer; mRNA — messenger ribonucleic acid; mTOR — mammalian rapamycin complex

Similar statements, however, were suspected since the 1970s, finally in 2005 British study confirmed the anticancer effect of metformin on breast cancer [8]. It led up to a new perspective of research on the non-diabetic effects of metformin intake — firstly in basic sciences, with secondary implementation to clinical trials. The following studies, finished by metanalyses, resulted in confirmation of the antitumor effect of metformin in breast cancer, but on the other hand — this effect cannot be considered universal. The results of metanalyses in lung cancer were inconclusive [9], and for endometrial and gastric cancers this effect was denied [10, 11]. Nowadays, the anti-cancer properties of metformin are widely considered [12]. This review aims to sum up the current knowledge on metformin usage in ATC.

Molecular mechanisms of antitumor metformin features

The molecular mechanism of the anticancer action of metformin is not completely understood. So far, two probable patterns of antitumor action of metformin have been suggested: it may act directly on cells or by modifying the metabolism [7, 13]. Those two possible mechanisms are presented in Figure 1.

The main direct mechanism of the anti-cancer action of metformin is the activation of the adenosine monophosphate-activated protein kinase (AMPK), which reduces cell division and arrests it in the G0/G1 phase of the cell cycle [6]. Biochemically, AMPK, or serine-threonine protein kinase, consists of a catalytic α subunit and two regulatory b and γ subunits. The factor affecting its activation is cellular stress. The protein kinase activated by AMP is responsible for maintaining cellular energy homeostasis. In addition, AMPK influences the growth, proliferation and differentiation of the body's cells through modulation of the mTOR (mammalian target of rapamycin complex) pathway. Two mTOR complexes have been described; mTORC1 and mTORC2, which are structurally and functionally distinct multiprotein complexes. mTORC1 leads to the stimulation of mRNA translation in the cell and ultimately controls its growth and proliferation. However, mTORC2 is one of the key factors involved in the regulation of actin cytoskeleton formation. Deregulation of mTOR plays a particular role in oncogenesis; disorders of the mTORC1 complex

result in uncontrolled cell growth and division, while mTORC2 abnormalities could lead to cancer metastasis [14, 15].

A direct anti-tumour effect of metformin is likely the regulation of the AMPK/mTOR system. Metformin leads to inhibition of the components of the respiratory chain starting with NADH/coenzyme Q dehydrogenase (complex I), which, under the influence of metformin, does not catalyse the oxidation reaction of NADH to NAD+, preventing the release of electrons necessary for further steps in the respiratory chain. As a result, the Krebs cycle, in which complex II participates, is inhibited and ATP synthesis in complex V is blocked. As a result of these changes, the cell is put into a state of oxidative stress. This state of the cell leads to the activation of AMPK. Activated AMPK leads to inhibition of the signalling pathways of the mTORC1, which limits its overexpression. This results in metformin-induced apoptosis of tumour cells. Additionally, by inhibiting the mTORC2 complex, metformin prevents metastasis formation [13, 15–17].

The indirect mechanism of action of metformin involves the inhibition of tumour progression by introducing metabolic changes in the body. The anti-tumour effect of metformin can be attributed to the sensitization of tissues to insulin, increased glucose uptake by muscles and reduced glucose secretion by the liver, which results in lower systemic glucose levels. Insufficient amount of glucose, involved in the metabolism of cells, including cancer cells, may affect their growth inhibition, without direct accumulation of the drug inside the cell [7, 13, 16].

Insulin resistance impact on thyroid cancer development

Argentinian research group, based on the HOMA-IR marker among patients with differentiated thyroid cancer (n = 20), in comparison to a euthyroid control group (n = 20), confirmed a significant association between thyroid cancer occurrence and insulin resistance, which was present among 56.3% of patients with papillary thyroid cancer and 25% of patients with follicular thyroid cancer [18].

Another research group from South Korea, analysed data of over 1000 females, and concluded that insulin resistance significantly increases the risk of follicular thyroid cancer, without impact on its clinical severity [19]. Similar results were formulated by a Chinese research group after comparing 153 cases of follicular thyroid cancer to 105 patients with benign thyroid lesions [20]. For papillary thyroid cancer, similar research was performed by a Turkish research group on 344 patients and 116 control subjects and resulted in a confirmed correlation between insulin resistance and this thyroid cancer subtype development [21].

Independent reviewers, concluding their review wrote about a noticeable correlation between insulin resistance and thyroid cancer risk, but they underline the need for further research on this issue [22].

Unfortunately, to the best knowledge of the authors, there is no study concerning the impact of insulin resistance on ATC.

Proapoptotic effect of metformin on cell lines

The antiproliferative effect of metformin on thyroid cancer cells was reported by many research groups, conducting *in vitro* research on cell lines derived from different histological types of thyroid cancer [23–25], including anaplastic thyroid cancer [26, 27]. The proapoptotic effect of metformin on the cell lines was observed in mice which were treated with oral metformin intake with secondary implantation of neoplasm cells [25, 28–30]. The cell cycle appeared to be stopped in G0/G1 phase after low doses of metformin in the medium, in the case of the cell lines derived from all histological subtypes of thyroid cancer (including anaplastic) [31]. The effect of metformin correlated with the level of glucose in the medium, but this correlation was confirmed for follicular and papillary carcinoma of the thyroid gland [32].

The usage of metformin in the prevention of thyroid cancer

In a meta-analysis focused on metformin usage in patients with insulin resistance and coexisting thyroid nodules, no significant difference in the change of lesion size between metformin users and the control group was confirmed. But on the other hand, the decrease in TSH level was correlated with changes in the HOMA-IR index [33]. Decrease of TSH after metformin intake was confirmed independently by the other research group [34].

The research conducted on the obese mouse model supports the thesis of the supportive effect of metformin in thyroid cancer prevention among the obese [35]. A South Korean cohort study conducted on 128 thousand people suggests that metformin may be useful in the prevention of thyroid cancer, but not in the early intervention [36]. Similar results were achieved in Taiwanese analyse performed on 1.4 million T2D patients — confirming the usage of metformin in thyroid cancer prevention [37]. On the other hand, in similar research from the UK conducted on 9 thousand people, none of the antidiabetic drugs (metformin, sulfonylureas, insulin therapy and thiazolidinediones) showed any decreasing effect on thyroid cancer incidence [38].

Metformin usage in thyroid cancer patients

In a large Korean study involving 223,530 individuals with T2D and newly diagnosed cancer, researchers investigated the effects of different glucose-lowering treatments on the development of cancer metastasis. The findings revealed that the use of dipeptidyl peptidase-4 (DPP-4) inhibitors did not significantly increase the risk of cancer spreading compared to no antidiabetic drug treatment, except in cases of thyroid cancer. However, treatment with metformin, either alone or in combination with DPP-4 inhibitors, was associated with a reduced risk of cancer metastasis in patients with pre-existing cancer, including thyroid cancer. These results suggest that metformin may have a protective effect in lowering the risk of cancer spreading in individuals with T2D and comorbid incident cancer, particularly in cases involving the thyroid [39]. National Institute of Health study appointed metformin as the only of the analysed factors (involving a high dosage of vitamin C and a ketogenic diet) as a useful adjuvant therapy in differentiated thyroid cancer with metastases [40].

In the bioinformatics research, based on ligand-receptor binding simulations, the synergistic effect of metformin and vemurafenib on anaplastic thyroid cancer cells was suggested. Then, the other research group confirmed this effect in *in vitro* research on cell lines [41, 42]. Similar results were achieved also for combinations of metformin with sorafenib [43], metformin with pioglitazone [26], and metformin with acetylsalicylate acid [44].

Retrospective research performed on 79 patients suggests that metformin-treated patients handle the therapy of iod-131 better in comparison to the control group. The advantages include smaller worsening of blood morphological parameters and faster regeneration. In the context of these results, metformin may be concerned as a radioprotective factor [45].

Conclusions

The beneficial effect of metformin on anaplastic thyroid cancer patients' treatment was confirmed, however, the mechanism of this interaction is still unclear. The usage of metformin in thyroid cancer prevention is still under discussion — nevertheless, studies conducted on larger groups support this beneficial impact, at least in patients with insulin resistance or metabolic syndrome. Both the synergistic effect of metformin in anaplastic thyroid cancer chemotherapy and its protective effect in radiotherapy are still concerns and need additional confirmation in randomized clinical trials.

Article information

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