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Review Articles

Could there be a role for the antidiabetic drug metformin in oncological treatment?

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Summary

Diabetes and tumour diseases are serious health problems in the elderly population. Several studies have suggested that patients with diabetes are at significantly higher risk of cancer. On the other hand, epidemiologic evidence suggests that some drugs used to treat hyperglycemia are associated with reduced risk of cancer. Metformin, the drug applied in type 2 diabetes, has been shown to reduce incidence and mortality due to malignant tumours in various localities. A hypothesis is presented which seeks to explain the anticancer effects of metformin. Empirical data from the scientific literature is used to support the hypothesis that metformin restricts the growth of human cancer stem cells (CSCs). The LKB1/AMPK (liver kinase B1/AMP activated protein kinase) mechanism of the antineoplastic action is pleiotropic, involving the activation of the LKB1/AMP pathway, which inhibits mTOR signalling, inhibits STAT-3 phosphorylation, arrests cell cycle at the G1 phase, inhibits cyclin D1 activity, reduces insulin levels, as well as IGF-1, TNFα, and IL-6 levels which reduce proliferation leading to apoptosis of neoplastic cells. In various tumours, including gynaecological cancers, metformin eliminates cancer stem cells (CSCs). Repositioning metformin as a possible antineoplastic option seems promising. The present authors suggest here that metformin could be a valuable tool for clinicians to help reduce cancer risk in elderly adults with diabetes.

Key words: Metformin; Ovarian cancer; Endometrial cancer; Cancer stem cells; Diabetes.

Introduction

Metformin, a biguanidine derivative (Figure 1), acquired from *Galega officinalis* seeds, is an herb that was already known in ancient Egypt [1]. For over 500 years it has been used in the treatment of type 2 diabetes, particularly in obese individuals. The prevalence of diabetes is dramatically increasing worldwide reaching epidemic proportion. Both diabetes and obesity constitute a global health problem in the 21st century, and are linked to the frequent manifestation of malignant tumours [2-4].

The results of numerous preclinical and clinical studies as well as increasing epidemiologic evidence suggests that metformin, one of the most favourable first-line antidiabetic drug, could inhibit cancer cell growth and proliferation and reduce all-cancer incidents [5-7]. By reducing the liver's blood glucose raising effect, metformin helps to lower blood glucose levels through the day (Figure 1). However here the authors would like to stress the antineoplastic benefit of this drug.

Hypothesis

Here the authors present a hypothesis that metformin-drug applied in type 2 diabetes can help control the metastasis of cancer *via* elimination of the cancer stem cells (CSCs) and may provide a new therapeutic direction against diabetes combined with malignant tumour.

The main assumptions of our hypothesis are: 1) elderly patients with diabetes and tumour diseases are very often represented in clinical practice, 2) new evidence from clinical studies has demonstrated the potential benefits of antidiabetic drug metformin on cancer therapy, 3) anticancer activity of metformin in the elderly has a remarkable clinical impact, 4) metformin restricts the growth of human cancer stem cells, and 5) elderly diabetic patients using metformin could have lower risk of dying from cancer compared with other patients in the same age group.

Epidemiologic evidence for a potentiating effect of metformin on cancer patient survival

Numerous populational studies have demonstrated that metformin used in the treatment of diabetes type 2 reduces both incidence and mortality due to malignant tumours in various localisations [5-12]. The results of studies in Scotland, which lasted for nine years and included over 11,000 patients with diabetes type 2, have documented a 23% reduction in morbidity due to malignant tumours in patients

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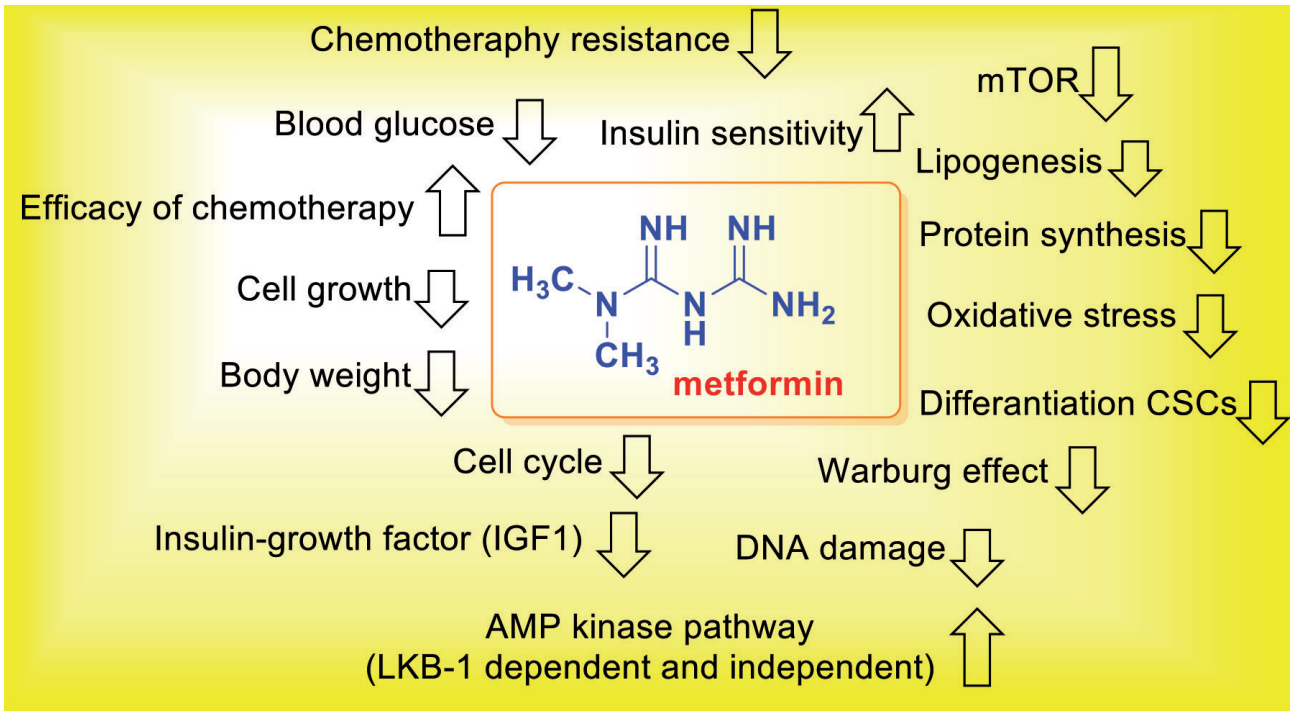

Figure 1. — Direct and indirect effects of metformin on cancer.

treated with metformin, as compared to those treated with derivatives of sulphonylurea [5]. Subsequent case-control type studies in Scotland, conducted on over 12,000 patients treated due to type 2 diabetes have shown that malignant tumours were detected in 7.3% of individuals treated with metformin, compared to 11.6% of those treated with other anti-diabetics [6]. Canadian epidemiological observations of over 10,000 patients with type 2 diabetes have demonstrated a reduction in mortality due to malignant tumours in metformin-treated patients with type 2 diabetes, as compared to patients treated with sulphonylurea derivatives and insulin (3.5% *vs*. 4.9% *vs*. 5.8%) [12].

Similar data have been revealed in the *ZODIAC* study in Holland: among over 1300 patients with type 2 diabetes, those treated with metformin manifested reduced mortality due to malignant tumours (HR 0.43), as compared to those treated with other anti-diabetic agents [13]. Gandini *et al.* [10] presented the results of a meta-analysis of databases including 65,540 diabetic patients diagnosed with cancer. In metformin-treated patients, morbidity was reduced by 31% (RR 0.69) and mortality by 34% (RR 0.66), compared to the patients treated with other anti-diabetic agents.

Response of cancer cells and cancer stem cells to metformin

The mechanism of the antineoplastic action of metformin is complex and involves several pathways of activity, mainly [14-18]: 1) activation of liver kinase B1/AMPK pathway. Activation of LKB1 by metformin involves AMPK which inhibits mTOR (mammalian target of rapamycin). This action results in the inhibition of protein synthesis, the inhibition of angiogenesis (due to reduced VEGF expression) and of cell proliferation, and a reduced expression of Glut-1 (glucose transporter type 1) and COX-2 which leads to cell apoptosis. 2) Direct inhibitory effect on mTOR with the consequences mentioned above. 3) Suppression of phosphorylation STAT3 (signal transducer and activator of transcription) involving expression of genes linked to cell survival, which results in their reduced proliferation and apoptosis. 4) Arrest of cell cycle at G1 phase and inhibition of cyclin D_1, which reduces cell proliferation. 5) Reduction in levels of circulating insulin and IGF1, exerting a mitogenic effect on neoplastic cells. 6) Reduced production of TNFα and IL-6 cytokines due to the inactivation of the nuclear kappa factor (NF_kB) and HIF-1α, which amplifies anti-inflammatory and anti-angiogenic effects. 7) Elimination of cancer stem cells, linked to cancer origin, resistance to chemo- and radiotherapy to tumour relapses and metastases.

Over the last decade metformin has been found to eradicate CSCs in various types of malignant tumours. In breast cancer it targets HER-2 positive cells of the CD44/CD24 phenotype, interacting with the monoclonal antibody of trastuzumab [19]. The inhibitory effect of metformin on CSCs has been demonstrated in various types of malignant tumours in *in vivo and in vitro studies* [20-22]. In ovarian cancer, the CSCs-eliminating action of metformin can be noted in the form of the reduced expression of -ALDH+, CD44+, and CD117+ markers, typical of ovarian cancer

and epithelial-mesenchymal transition (EMT) [23].

In their review paper, Dilokthornsakul *et al.* (24) quoted the results of two retrospective studies on patients with ovarian cancer additionally treated with metformin. In metformin-treated patients (72 patients) five-year survival was noted in 73% cases, as compared to 44% (143 patients) who did not receive metformin ($p = 0.0002$). No effect of tumour advancement according to FIGO was detected. The second of the two retrospective studies on women suffering from diabetes and ovarian cancer (341 patients) confirmed the favourable effect of metformin on survival: 63% of women using metformin survived five years as compared to 23% women treated with other anti-diabetics.

Studies by Hirsch *et al.* [22] have suggested that metformin eliminated CSCs, acting synergistically with chemotherapy. Such an effect of metformin on the suppression and eradication of CSCs has also been presented by Gadducci *et al.* [14] in various "gynaecological" cancers, including endometrial cancer.

According to the studies related to the effect of metformin on the course of endometrial cancer, both progression free survival and overall survival have shown significant extension. Metformin mainly reduced the ability of endometrial cancer cells to migrate and, therefore, to metastasize [25, 26]. Repositioning metformin as a possible antineoplastic option seems promising and suggests that metformin might improve cancer prognosis. [14, 15, 24-27].

Conclusion

According to several papers discussed above, the use of metformin in the treatment of gynaecological cancers (but not only) may provide a new, additional therapy option. The present authors suggest that metformin could be a valuable tool for clinicians to help reduce cancer risk in the elderly with diabetes.

References

[1] Baley C.J., Day C.: "Metformin: its botanical background". *Pract. Diab. Int.*, 2014, *21*, 115.

[2] Rosta A.: "Diabetes and cancer risk: oncologic considerations". *Orv. Hetil.*, 2011, *152*, 1144.

[3] Arnold M., Pandeya N., Byrnes G., Renehan P.A.G., Stevens G.A., Ezzati PM. *et al.*: "Global burden of cancer attributable to high body-mass index in 2012: a population-based study". *Lancet Oncol.*, 2015, *16*, 36.

[4] Drake I., Gullberg B., Sonestedt E., Stocks T., Bjartell A., Wirfalt E. *et al.*: "Type 2 diabetes, adiposity and cancer morbidity and mortality risk taking into account competing risk of noncancer deaths in a prospective cohort setting". *Int. J. Cancer*, 2017, *141*, 1170.

[5] Evans J.M., Donnelly L.A., Emslie-Smith A.M., Alessi D.R., Morris A.D.: "Metformin and reduced risk of cancer in diabetic patients". *BMJ*, 2005, *330*, 1304.

[6] Libby G., Donnelly L.A., Donnan P.T., Alessi D.R., Morris A.D., Evans J.M.: "New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes". *Diabetes Care*, 2009, *32*, 1620.

[7] Daugan M., Dufaÿ Wojcicki A., d'Hayer B., Boudy V.: "Metformin: An anti-diabetic drug to fight cancer". *Pharmacol. Res.*, 2016, *113*, 675.

[8] Zhou X.L., Xue W.H., Ding X.F., Li L.F., Dou M.M., Zhang W.J., *et* al.: "Association between metformin and the risk of gastric cancer in patients with type 2 diabetes mellitus: a meta-analysis of cohort studies". *Oncotarget*, 2017, *8*, 55622.

[9] Decensi A., Puntoni M., Goodwin P., Cazzaniga M., Gennari A., Bonanni B., *et al.*: "Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis". *Cancer Prev. Res. (Phila.)*, 2010, *3*, 1451.

[10] Gandini S., Puntoni M., Heckman-Stoddard BM., Dunn BK., Ford L., DeCensi A. *et al.*: "Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders". *Cancer Prev. Res. (Phila.)*, 2014, *7*, 867.

[11] Zhang P., Li H., Tan X., Chen L., Wang S.: "Association of metformin use with cancer incidence and mortality: a meta-analysis". *Cancer Epidemiol.*, 2013, *37*, 207.

[12] Bowker S.L., Majumdar S.R., Veugelers P., Johnson J.A.: "Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin". *Diabetes Care*, 2006, *29*, 254.

[13] Landman G.W., Kleefstra N., van Hateren K.J., Groenier K.H., Gans R.O., Bilo H.J.: "Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16". *Diabetes Care*, 2010, *33*, 322.

[14] Gadduci A., Biglia N., Tana R., Cosio S., Gallo M.: "Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning". *Crit. Rev. Oncol. Hematol.*, 2016, *105*, 73.

[15] Del Barco S., Vazquez-Martin A., Cufí S., Oliveras-Ferraros C., Bosch-Barrera J., Joven J., *et al.*: "Metformin: multi-faceted protection against cancer". *Oncotarget*, 2011, *2*, 896.

[16] Dowling R.J., Goodwin P.J., Stambolic V.: "Understanding the benefit of metformin use in cancer treatment". *BMC Med.*, 2011, *9*, 33.

[17] Vallianou N.G., Evangelopoulos A., Kazazis C.: "Metformin and cancer". *Rev. Diabet. Stud.*, 2013, *10*, 228.

[18] Feng F., Zhang J., Fan X., Yuan F., Jiang Y., Lu R., *et al.*: "Down-regulation of Rab27A contributes to metformin-induced suppression of breast cancer stem cells". *Oncol. Lett.*, 2017, *14*, 2947.

[19] Vazquez-Martin A., Oliveras-Ferraros C., Menendez J.A.: "The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells". *Cell Cycle*, 2009, *8*, 88.

[20] Bao B., Azmi AS., Ali S., Zaiem F., Sarkar F.H.: "Metformin may function as anti-cancer agent via targeting cancer stem cells: the potential biological significance of tumor-associated miRNAs in breast and pancreatic cancers". A*nn. Transl. Med.*, 2014, *2*, 59.

[21] Shank J.J., Yang K., Ghannam J., Cabrera L., Johnston C.J., Reynolds R.K., et al.: "Metformin targets ovarian cancer stem cells in vitro and in vivo". *Gynecol. Oncol.*, 2012, *127*, 390.

[22] Hirsch H.A., Iliopoulos D., Tsichlis P.N., Struhl K.: "Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission". *Cancer Res.*, 2009, *69*, 7507.

[23] Zhang R., Zhang P., Wang H., Hou D., Li W., Xiao G., *et al.*: "Inhibitory effects of metformin at low concentration on epithelial-mesenchymal transition of CD44(+)CD117(+) ovarian cancer stem cells". *Stem Cell Res. Ther.*, 2015, *6*, 262.

[24] Dilokthornsakul P., Chaiyakunapruk N., Termrungruaglert W., Pratoomsoot C., Saokaew S., Sruamsiri R.: "The effects of metformin on ovarian cancer. A systematic review". *Int. J. Gynecol. Cancer,* 2013, *23*, 1544.

[25] Meireles C.G., Pereira S.A., Valadares L.P., Rêgo D.F., Simeoni L.A., Guerra E.N.S., *et al.*: "Effects of metformin on endometrial cancer: Systematic review and metaanalysis". *Gynecol. Oncol.*, 2017, *147*, 167.

[26] de Barros Machado A., Dos Reis V., Weber S., Jauckus J., Brum I.S., von Eye Corleta H., *et al.*: "Proliferation and metastatic potential of endometrial cancer cells in response to metformin treatment in a high

versus normal glucose environment". *Oncol. Lett.*, 2016, *12*, 3626.
[27] Irie H., Banno K., Yanokura M., Iida M., Adachi M., Nakamura K., *et al.*: "Metformin: A candidate for the treatment of gynecological tumors based on drug repositioning". *Oncol. Lett.*, 2016, *11*, 1287.

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