Metformin and oral squamous cell carcinoma?

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Abstract

Introduction

Recently, more evidence has been presented for the potential anti-cancer effect of metformin, a drug used successfully to treat diabetes mellitus. Therefore, the aim of this study was twofold: to compare diabetic patients with oral cancer who were treated with metformin to non-diabetic patients with oral cancer who did not receive metformin treatment, and to provide a review of the current literature in regard to oral cancer.

Materials and methods

Files of all patients treated for oral cancer at the Department of Craniomaxillofacial and Oral Surgery, University Hospital Zurich between January 2007 and August 2012 were evaluated retrospectively. Age, gender distribution, and presence of metformin-treated, type 2 diabetes were taken into consideration.

Results

A total of 154 patients were treated (91 male and 63 female); their median age was 63.7 years (24-89 years). Six patients (3.9%) had diabetes; of those, 2 (1.3%) were treated with insulin and 4 (2.6%) with metformin.

Conclusion

A lower prevalence of oral cancer was found in diabetic patients being treated with metformin, but further studies need to be performed with a larger population.

Introduction

Recently, increasing evidence has been presented for the potential anti-cancer and anti-metastasis effect of metformin, the most widely used drug for type 2 diabetes in the world. Metformin was first described by Werner and Well in 1922, and its glucose-reducing effect was first described in 1929 by Slotta and Tschesche1. Metformin seems to activate AMPK, inhibit tumour growth, and reduce the insulin level, which acts as a tumour-promoting factor. In 2009, Hirsch et al. described metformin as selectively targeting cancer stem cells and acting, therefore, in combination with chemotherapy to block tumour growth2.

It has also been discussed that metformin inhibits the epithelial-mesenchymal transition (EMT)3,4. The EMT is defined as a process by which epithelial cells lose their polarity and are converted to a mesenchymal phenotype. EMT occurs in embryogenesis and is characterized by down-regulation of E-cadherin expression (cell-cell adhesion) and up-regulation of vimentin, N-cadherin, and fibronectin4. Furthermore, hypoxia probably leads to EMT5. It could be shown that the regression of E-cadherin and up-regulation of mesenchymal markers lead to a worse tumour prognosis for different kind of cancers, including breast cancer6-7, oesophageal cancer8, renal cell carcinoma9, small cell lung cancer10, and oral cancer11,12,13.

Population-based studies of type 2 diabetic patients14,15 have induced that metformin reduces the incidence of different kinds of cancer, including in breast16,17, colon18 and liver19. Recently, it has also been suggested that metformin is associated with a lower risk of cancer compared with cumulative exposure to sulfonylurea derivatives20. Studies dealing with the incidence of oral cancer and metformin treatment for type 2 diabetic patients are still missing. Therefore, the aim of the current study was to evaluate the portion of patients receiving metformin treatment for type 2 diabetes in relation to the appearance of oral cancer.

Materials and methods

This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

All files of patients with oral squamous cell carcinoma who were treated between January 2007 and August 2012 were systematically reviewed and retrospectively evaluated. Data regarding age, gender, and presence of diabetes mellitus and treatment with metformin were taken into account, analysed, and compared to current literature.

Results

A total of 154 patients were treated between January 2007 and August 2012 at the Department of Craniomaxillofacial and Oral Surgery, University Hospital Zurich. The gender distribution was 91:63 (male:female) (Figure 1). The mean age was 63.7 years (24-89 years) (Figure 1). The mean age was 63.7 years (24-89 years) (Figure 1).

Of the 154 patients, 6 had diabetes mellitus; of the diabetic patients, 2 were treated with insulin, and 4 (2.6%) with metformin. The median length of time during which a patient received metformin treatment was 4.2 years.

Discussion

Shaw JE et al. estimated the worldwide prevalence of diabetes between 2010 and 2030 based on studies from 91 countries21. The highest prevalence for 2010 was found in India, with 7.1% adjusted to the national population;
Europe, with 6.9%; Portugal, with 12.2%; Germany, with 12.0%, and the United States, with 12.0%. In the present small study of 154 tumour patients, 3.9% had diabetes. However, this population included a high number of elderly patients with a median age of 63.7 years; therefore, a higher number of diabetes patients would be expected. In regard to head and neck squamous cell carcinoma cells, Sandulache et al. concluded that these tumour cells are dependent on glucose rather than glutamine for energy production and survival, and they suggested that the presence of wild-type p53 can partially protect tumour cells. These findings were in agreement with those of Vitale-Cross et al. for premalignant oral lesions in the mouse model. They observed that metformin stimulated the AMP-activated protein kinase (AMPK), leading to a reduced mammalian target of rapamycin complex 1 (mTORC1) activity, particularly in the basal proliferating epithelial layer of these oral premalignant lesions. In line with these findings, Patel et al. reported that in addition to reducing mTORC1 activity, metformin inhibits OCT-3 expression in oral premalignant lesions.

In regard to oral cancer and radio- or chemotherapy, it is of great interest whether these therapy options in combination with metformin improve survival and prognosis. For lung and breast cancer cell lines, it has been shown that metformin in combination with paclitaxel induces cell cycle arrest. Studying ovarian cancer using a nude mice model, Rattan et al. found that metformin treatment inhibited the growth of metastatic nodules in the lung and significantly potentiated cisplatin cytotoxicity, resulting in an approximately 90% reduction in tumour growth compared with treatment by either of the drugs alone. Furthermore, the combination of metformin and doxorubicin has been found to prevent relapse in xenografts generated with prostate and lung cancer cell lines. For prostate cancer, Colguhoun et al. stated that combining bicalutamide and metformin significantly reduces prostate cancer cell growth more than either monotherapy does.

In regard to radiotherapy, very few information is available. Liu et al. have shown that the combination of a low concentration of metformin and radiotherapy results in a considerable enhancement of cytotoxic effects in human hepatoma cell lines, leading to decreased DNA repair by reducing ATP production. Song et al. found that metformin increases the radiosensitivity of human breast cancer cells. So far, for head and neck cancer, the effect of either radio- or chemotherapy in combination with metformin has not been the subject of available studies.

**Conclusion**

The prevalence of diabetes in all oral cancer patients was lower compared to the general population. However, there is still a need for further epidemiologic, multicentre studies.

### References


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