Oral Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Effects of metformin on head and neck cancer: A systematic review

Daniela Fortunato Rêgo [a], Ludmila Madeira Cardoso Pavan [a], Silvia Taveira Elias [a], Graziela De Luca Canto [b,c], Eliete Neves Silva Guerra [a,*]

[a] Oral Histopathology Laboratory, Health Sciences Faculty, University of Brasília, Brasília, Brazil
[b] Department of Dentistry, Federal University of Santa Catarina, Florianópolis, Brazil
[c] Department of Dentistry, University of Alberta, Edmonton, Canada

ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 9 January 2015
Accepted 11 January 2015
Available online xxxx

Keywords:
Evidence-based medicine
Head and neck
Metformin
Squamous cell carcinoma
Systematic review

SUMMARY

Conventional therapeutic approaches for head and neck squamous cell carcinoma (HNSCC) are associated with many adverse effects that reduce quality of life. Therefore, identification of new less cytotoxic treatments is highly important. Metformin, which is commonly used for type 2 diabetes, may reduce cancer risk. A few clinical studies have examined the association between HNSCC and metformin. Therefore, the aim of this systematic review was to synthesize the available literature of the potential effect of metformin on HNSCC. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Studies were gathered by searching PubMed, MEDLINE, EMBASE, LILACS, and the Cochrane database before June 28, 2014, with no time or language restrictions. Studies that evaluated individuals of any age that underwent metformin and had HNSCC and compared with patients without treatment or patients that use other kind of treatment for HNSCC (drugs or radiotherapy) were considered. Selected articles were evaluated according to the Critical Appraisal Skills Programs. Of 313 identified citations, 3 studies met the inclusion criteria and were used for qualitative analysis. These studies demonstrated that individuals taking metformin had decreased rates of locoregional recurrence and metastasis and improved overall survival and disease-free survival rates. Individuals taking metformin had a lower incidence of HNSCC than those not taking metformin. Though there are only a few studies on the topic, currently available evidence suggests an association between HNSCC and metformin use. Metformin reportedly improves the overall survival of HNSCC patients.

Introduction

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide derived from the French lilac (*Galega officinalis*). Several centuries ago, it was discovered that French lilac reduces the symptoms of diabetes mellitus [1]. Approximately 120 million people use metformin worldwide [2] and it is low-cost [3]. It is indicated for treatment of type 2 diabetes, and also used for polycystic ovarian syndrome, metabolic syndrome, and diabetes prevention [4,5]. The most evident side effects so far reporter are nausea and diarrhea [6].

The use of metformin in diabetic patients has been associated with significantly lower risks of cancer incidence and mortality [7–9]. Recent retrospective analyses indicate that metformin inhibits cell proliferation in several human malignancies, including gastric carcinoma [10], pancreatic cancer [11], medullary thyroid cancer [12] and endometrial carcinoma [13]. It is also described that metformin suppresses tumor growth in animal models of ovarian cancer [14], melanoma [15], prostate cancer [16] and breast carcinoma [17]. Furthermore, this drug was also found to be associated with improved overall survival among diabetic patients with breast, prostate, colorectal or head and neck cancer [9,18–21]. Although Decensi et al. [3] in 2010 performed a systematic review and meta-analysis on metformin and cancer risk in diabetic patients, they did not analyze head and neck cancer patients. Indeed, little is known about the potential effect of metformin on head and neck cancer patients, which makes a systematic review on this subject required.

Results from epidemiologic surveys confirm that metformin has significant effects on tumorigenesis [22,23]. The antineoplastic activity of metformin depends on the metabolic characteristics of patients and the molecular pathology of tumors. Adenosine monophosphate-activated protein kinase (AMPK) is the main mediator

* Corresponding author at: SQN 205, bloco H apto 201, Asa Norte, Brasília, DF 70843-080, Brazil. Tel.: +55 61 96684988.
E-mail addresses: dani.se.ela@gmail.com (D.F. Rêgo), ludmadeira@hotmail.com (L.M.C. Pavan), silvinhaelias@hotmail.com (S.T. Elias), delucacanto@gmail.com (G. De Luca Canto), elieteneves@unb.br (E.N.S. Guerra).

http://dx.doi.org/10.1016/j.oraloncology.2015.01.007
1368-8375/

of the anticancer effects of metformin, though other mechanisms have also been described. Activation of AMPK has been proposed as the main direct mechanism by which metformin inhibits tumor growth. This enzyme influences cellular energy homeostasis, acting as a metabolic master switch that regulates several intracellular systems [24–26].

Oral and pharyngeal cancer, grouped together, are the sixth most common type of cancer in the world [27]. Moreover, the concept of using metformin as a chemopreventive agent to control head and neck carcinogenesis is promising [10,11,28]. Therefore, the aim of this systematic review was to synthesize the available literature of the potential effect of metformin on HNSCC.

Materials and methods

This systematic review was conducted following as closely as possible the PRISMA checklist [29]. We did not register a protocol.

Eligibility criteria

We selected articles that dealt primarily with the effect of metformin on HNSCC located in the lip and/or oral cavity, pharynx, larynx, nasal cavity, or paranasal sinuses [30]. Studies that evaluated individuals of any age that underwent metformin and had HNSCC and compared with patients without treatment or patients that use other kind of treatment for HNSCC (drugs or radiotherapy) were considered. The study design included randomized or non-randomized clinical trials, cohort studies, and case-control studies.

Studies were excluded for the following reasons: (1) different target conditions, such as metformin was not used as a coadjutant in cancer treatment; (2) reviews, letters, personal opinions, book chapters, and conference abstracts; and (3) associations between metformin and HNSCC treatment in experimental studies (*in vitro* or *in vivo* animal studies) and clinical trials (phase 1, 2, or 3).

Information sources and search strategy

Studies to be considered for inclusion were identified using a search strategy for each electronic bibliographic database: the Cochrane Library, EMBASE, MEDLINE, LILACS (Literatura Latino Americana em Ciências da Saúde), and PubMed (Appendix 1). The reference list will be checked at the end of search. We conducted all searches across all databases from the beginning dates through June 28, 2014. We managed the references manually and removed duplicate hits.

Study selection

We selected articles for inclusion in 2 phases. In phase 1, 2 authors (D.F.R. and S.T.E.) independently reviewed the titles and abstracts of all the references. These authors selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, 2 authors (D.F.R. and S.T.E.) read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. The same 2 authors independently reviewed all full text articles. Any disagreements in the first or second phases were resolved by discussion and mutual agreement between the 2 authors. If the 2 authors could not reach a consensus, a third author (E.N.S.G.) was involved to make a final decision.

Data collection process and items

One author (D.F.R.) collected the required information from the selected articles: authors, year of publication, country, main objective, study design, source population, setting, register or hospital, median age, samples, referenced group, adjusting variables, results and main conclusions. A second author (S.T.E.) crosschecked all the retrieved information. Again, any disagreements were resolved by discussion and mutual agreement between the 2 authors. The third author (E.N.S.G.) became involved, when required, to make a final decision.

Risk of bias in individual studies

The authors methodologically appraised all of the selected studies according to a modified check list based on the Critical Appraisal Skills Programs (CASP) [31]. No attempt was made to validate the selected criteria. Two reviewers (D.F.R and E.N.S.G.) answered 12 questions that were able to assess the quality of the included studies. In the end, the articles were categorized as "high," "low," or "moderate" according to the analysis of each study. Disagreements between the 2 reviewers were resolved by a third reviewer (S.T.E).

Summary measures

Any outcome measurements were considered in this review (risk ratios, odds ratios [OR], or risk differences for dichotomous outcomes; mean differences or standardized mean differences for continuous outcomes).

Synthesis of results

A meta-analysis was planned since the data from the included studies was considered relatively homogeneous.

Risk of bias across studies

Only to be applied if meta-analysis was possible.

Results

Study selection

In phase 1 of study selection, 313 citations were identified across the five electronic databases. After the duplicate articles were removed, only 262 citations reminded. Comprehensive evaluation of the abstracts was completed and 238 articles were excluded, so 24 articles remained after phase 1. No additional studies from the reference lists of the identified studies. From the 24 articles retrieved to conduct a full text review. This process led to exclusion of 21 studies (Appendix 2, [56–65]). In the end, only 3 articles [9,20,21] were selected. A flow chart detailing the process of identification, inclusion, and exclusion of studies is shown in Fig. 1.

Study characteristics

The studies were conducted in 2 different countries: the United States of America [9,20] and Taiwan [21]. All 3 studies were published recently (1 article in 2012 and 2 articles in 2014) and were written in English. All selected articles were prospective cohort studies. A summary of descriptive characteristics for the studies is given in Table 1.

Risk of bias within studies

The reported methodological quality of the 3 included studies is outlined in Table 2. Included studies ranged from moderate to high risk of potential bias. Common weaknesses identified were: failure

Please cite this article in press as: Rêgo DF et al. Effects of metformin on head and neck cancer: A systematic review. Oral Oncol (2015), http://dx.doi.org/10.1016/j.oraloncology.2015.01.007