

REVIEWER #1

The manuscript by Wu and colleagues describes a scoping review of the literature on the influence of the hypothalamic-pituitary-thyroid (HPT) axis on normal and cancerous oral tissue. Pubmed and Scopus databases were searched for articles investigating the effect of thyroid hormone and its receptor in oral tissues or cell lines. Fourteen studies were identified thus. Data from the studies were presented by loss of heterozygosity in thyroid hormone receptor gene, thyroid hormone receptor RNA expression, epigenetic modification of thyrotropin releasing hormone gene, antibody levels against thyroid stimulating hormone, exogenous thyroid hormone stimulations, correlation between thyroid stimulating hormone and disease outcome, and proliferation following thyroid hormone stimulation. From the results, the authors conclude that there is validity in investigating the expression of HPT components by oral mucosa cells.

General comments:

- The overall premise of the review seems odd to me. The others clearly identify a gap of knowledge without scoping the literature (line 52f). Would the best way to answer this not be a study examining the effect of HPT component production by oral tissue rather than examining the limited literature that will not allow you to make adequate conclusions?

Many thanks for this comment. Coming to conclusion without systematically appraising the literature may lead to bias and may erroneously led the authors to design a study when there is no real need. At the same time, existing literature on this topic is not so rich as to allow the design of a systematic review type question (i.e., narrow, specific question aiming at a well-defined answer), hence a scoping review (broader scope, wider question/answer) design was chosen. Whilst others may have already identified a gap of knowledge based on their own perceptions and knowledge, this present work clearly and systematically reaches this conclusion based on predefined criteria in a more objective and reproducible way. The results show that whilst oral cells respond to HPT axis components, currently there is no evidence of the production of HPT axis components *by* oral tissues. This result allow us to identify a specific knowledge gap that will be filled by testing the production of HPT components by oral cells.

- Some of the summarized results are based on a single study (section 2.2.2; 2.2.3; 2.2.6; and 2.2.7). Section 2.2.5 cites four papers, but all are from the same group. This diminishes their impact dramatically and may not warrant its own results section.

The research design we employed (scoping review) is made of a series of well-defined, transparent and reproducible screening steps. All the data resulting from these screening steps must be shown, regardless of their perceived credibility or impact. Unlike a systematic review, a scoping review does not necessarily assess the risk of bias of individual studies. Furthermore, the fact that certain results are produced by the same group does not automatically diminish their value.

- The authors seem to make no distinction if the results they are summarizing are obtained from patient samples, primary cells, or are from cell lines. There are also several studies that seem to indicate HNCC tumors rather than specifically OSCC cancerous lesions.

Thanks for this remark. Table 1 reports the following study details for each article included:

Type of study, Population/ Specimen, Intervention, Control, Outcome, Biomarkers, Assay methodology. Specifically, the origin of the sample are reported in the section Population/Specimen. We hope this satisfactorily addresses your comment.

Whilst the table is intended to provide sufficient details for each study (including whether the samples are obtained from patient samples, primary cells, or are from cell lines), the results section only summarises the overall significance of these findings in an attempt to avoid repetition.

Specific comments:

- From table 1 it looks like there are three steps in the screening process. The second and third step are adequately explained of why rejections were made at that point, however, there seems to be no criteria that described exclusion at this point or the data that the Cohen kappa analysis was based on.

Thanks for this comment – we assume that the referee refers to Figure 1. Same inclusion and exclusion criteria were used throughout the screening and selection process and are specified in 4.2.

Regarding the results used to calculate Cohen kappa, the data for Cohen kappa analysis are now included as Supplementary table 1 (line 90). Original Supplementary table 1 is now supplementary table 2 (line 156).

- Line 156 indicates a Table 3, but there is no Table 3 in the manuscript.

Thanks - this has also been fixed as supplementary table 2.

- The final sentence in the discussion the use of the word equivalent is confusing to me. Are the authors proposing that the amount of HPT hormones produced by the oral mucosa is equivalent to the endocrines produced by the actual HPT organs?

Thanks for this comment. Authors are proposing that the oral mucosa might be able to act as a local HPT axis equivalent, producing HPT hormones and also being targets of these hormones. Thus, it would be worth investigating (added local to line 327). The terms “equivalent”, “homolog”, “analog/ue” are widely used to indicate that the tissue under investigation (e.g. skin) has the enzymatic machinery necessary to produce molecules that are typical of another organ/system, e.g. HPA equivalent <https://pubmed.ncbi.nlm.nih.gov/27061711/>

- The authors indicate supplementary data, but these were not available for the review.

Supplementary data are now attached for review