Early View

Research letter

Oral inflammation and FeNO: a cross-sectional study

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Oral inflammation and FeNO: a cross-sectional study

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Take home message (256-character (including spaces))
Oral inflammation is not associated with increased FeNO levels in non-asthmatic children and adolescents. The observed inverse association that gingival bleeding might decrease FeNO needs more studies to confirm.
To the Editor:
Fractional exhaled nitric oxide (FeNO) is a quantitative and non-invasive marker of respiratory inflammation and airway hyperresponsiveness [1]. NO is formed by cells of the airway mucosa and via the inducible nitric oxide synthase (NOS) with L-arginine as a substrate [2]. Measurements of FeNO can provide an indicator of type 2 airway inflammation and might be used for diagnosis and management of diseases, especially asthma [1], although this notion was not fully supported by a recent randomised controlled trial [3].
FeNO levels have several well-established and suggested determinants, including physiological factors, e.g., age and sex, as well as diet, smoking, medication, and infection [1]. Despite the mounting studies on FeNO per se and its clinical application, only one small interventional study with adult asthmatic patients showed decreased FeNO levels after oral care (gargle with water and brush teeth) [4]. However, the role of oral inflammation and FeNO in the general population is unclear.
Periodontal diseases, like gingivitis or periodontitis, could trigger low-grade systemic inflammation [5]. In addition, aspiration of dental plaque or bacterial components and circulation of periodontal bacteria may ignite the succeeding inflammatory response [6]. Our previous research found that poor oral health is associated with declined lung function in adolescents [7]. In this line of thought, it is plausible to explore whether oral inflammation could also affect FeNO levels in children and adolescents, which are generally healthy populations. Considering the existing results [4], we hypothesised that poor oral condition could result in higher FeNO levels.
Our study was based on healthy, full-term German newborns that were recruited from 1995 to 1999 in the Munich study centre of the two German birth cohorts: "German Infant study on the influence of a Nutritional Intervention plus environmental and genetic influences on allergy development" (GINIplus) and "influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany" (LISA). Details on the two population-based cohorts have been previously described [8]. Relevant ethical approval and written informed consent regarding the studies were acquired aforehand.
The present cross-sectional analysis in non-asthmatics included 449 children aged 10 and 891 adolescents aged 15 years with completed information on FeNO and dental examination. FeNO was measured using the NIOX MINO® (Aerocrine, Sweden) as described before [9, 10]. Dental examination has also been described previously in detail [11]. Briefly, a blunt probe was used to measure the sulcus bleeding index (SBI), and a total score was determined according to the sulcus bleeding status of each sextant; we did not check the periodontal pockets because of the young age of the participants. The SBI ranged from 0, meaning no bleeding, to 6, indicating all sextants were affected indicating possibly severe inflammation.
FeNO data were In-transformed (natural logarithm) to normalise the distribution. We built linear regression models to analyse the association between FeNO and oral inflammation (represented by SBI categorised into none, 1-3 and 4-6 affected sextants). The models were adjusted for study, sex, age, body mass index, and parental educational level. Sensitivity analyses excluded active smokers in the 15-year group and participants with FeNO levels close to the lower detection limit of the device (below 10%, which corresponded to a FeNO level of 6 ppb, near the device lower detection limit of 5 ppb). In addition, we stratified the main model by three levels of high sensitivity serum C-reactive protein (hs-CRP), a marker of systemic inflammation. All analyses were performed via R 4.1.3 (https://www.R-project.org/).

Regarding the children aged 10 years, FeNO levels (ppb, geometric means, and standard deviations in parenthesis) were 15.9 (1.9), 13.1 (2.2) and 13.3 (2.2) for the three SBI categories: none, 1-3, and 4-6, respectively. These metrics were 20.5 (1.8), 19.3 (1.9) and 20.9 (1.8) for the 15-years.

Crude comparisons showed that FeNO levels did not increase with the elevated SBI categories or oral inflammation levels neither for the 10 years old children nor the 15 years old adolescents. The adjusted models also showed that SBI categories were not correlated with increased levels of FeNO (Table 1). They were even statistically significantly associated with decreased FeNO levels in 10-year-old children. The effect estimates for the 15-years did not exceed the statistical significance threshold. The association was not qualitatively affected by any of the sensitivity analyses (data not shown).

Our results were not in line with our primary hypothesis that oral inflammation may be associated with increased levels of FeNO. However, we should be cautious about concluding any opposite association for several reasons. First, the observed significant inverse association between poor oral health and FeNO was strongly driven by subjects with very low FeNO, which was below 6 ppb. The exclusion of those subjects with such FeNO concentrations tuned the association down to null. Thus, the significant inverse association might be interpreted as an artefact, because no plausible explanation for the finding in this subgroup of very low FeNO levels could be identified. However, the artificial exclusion of the low FeNO subjects without any sound reasons may bias the overall association.

Second, a recent systematic review of three studies reported higher saliva NO levels in the group of adults with chronic periodontitis compared to the periodontally healthy group [12]. FeNO levels are lower in smokers due to a potential negative feedback effect of the NO from cigarette smoke [13, 14]. Hence, one might speculate that our observed association might be a result of a potential negative feedback mechanism of oral cavity-originated NO. However, we were unable to differentiate the NO sources and failed to verify this hypothesis.
Third, type 2 or eosinophilic inflammation is linked with FeNO, while neutrophilic inflammation usually links to the production of oxidant species that may react with endogenous NO and reduce its concentration [15]. Unfortunately, our data were insufficient to differentiate between eosinophilic and neutrophilic inflammation, even though our stratified analysis for the low, medium, and high CRP levels showed similar associations between oral inflammation and FeNO levels across strata.

Our study exhibits two main strengths: a large sample size consisting of an almost non-smoking population and robust associations across several sensitivity analyses. Nevertheless, the limitations of the cross-sectional design and potential selection bias cannot be neglected. The 5 ppb lower detection limit precluded us from checking the association at all FeNO levels. Moreover, we were uncertain about the clinical meaning of the generally low FeNO levels, and the generalizability of our study might be limited to children or adolescents. Hence, more longitudinal population-based studies and well-designed trials are warranted, thereby clarifying the association between oral inflammation and FeNO.

Summarising the strengths and weakness of this study and the attempts to interpret the findings, we conclude that oral inflammation is not associated with increased FeNO levels in non-asthmatic children and adolescents. In addition, we deem that more studies are needed before drawing a sound conclusion about the inverse association.
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Conflict of interest
The authors declare that they do not have any competing interests

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Table 1. Linear regression results on association between oral inflammation and exhaled nitric oxide fraction (FeNO)

<table>
<thead>
<tr>
<th>SBI categories</th>
<th>n</th>
<th>Means ratio</th>
<th>95% CI</th>
<th>p-value</th>
<th>n</th>
<th>Means ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>449</td>
<td>Ref</td>
<td></td>
<td></td>
<td>891</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>327</td>
<td>0.80</td>
<td>0.73 – 0.88</td>
<td>&lt;0.001</td>
<td>148</td>
<td>0.94</td>
<td>0.85 – 1.04</td>
<td>0.232</td>
</tr>
<tr>
<td>4-6</td>
<td>258</td>
<td>0.82</td>
<td>0.73 – 0.92</td>
<td>&lt;0.001</td>
<td>100</td>
<td>0.99</td>
<td>0.89 – 1.12</td>
<td>0.982</td>
</tr>
</tbody>
</table>

Bold indicates statistically significant results.

CI: confidence interval; Ref: reference; SBI: sulcus bleeding index.

Adjusted for study, sex, age, body mass index, and parental educational level. Means ratios were back-transformed from the log (natural logarithm, ln) transformation of FeNO data. Their interpretation is similar to that of odds ratios.
References

Conflict of Interest: All authors have nothing to disclose.