Association Between Glycemia, Serum Lipoproteins, and the Risk of Oral Leukoplakia

The population-based Study of Health in Pomerania (SHIP)

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OBJECTIVE — Oral leukoplakia is an oral lesion with a premalignant character. Besides smoking and alcohol, diabetes could be a risk factor. The aim is to search for such an association.

RESEARCH DESIGN AND METHODS — Subjects with leukoplakia (N = 123) from the population-based Study of Health in Pomerania (SHIP) were matched 1:2 for age and sex with unaffected control subjects. Behavioral and lifestyle factors were assessed by a questionnaire. Lipoprotein concentrations, glycemia, and inflammation parameters were determined.

RESULTS — Subjects with oral leukoplakia showed higher levels of diabetes-related metabolites, a higher LDL/HDL cholesterol ratio (P = 0.004), and higher A1C (P = 0.002), and they were more frequently smokers (P < 0.001). Assessed by conditional logistic regression, the probability of leukoplakia increases with current smoking (odds ratio 2.20 [95% CI 1.16–4.17]) and higher levels of A1C (1.51 [95% CI 1.08–2.12]), revealing interaction between both factors (P = 0.012).

CONCLUSIONS — Diabetes is associated with the risk of oral leukoplakia, which is exaggerated by smoking. The risk is positively correlated with A1C concentrations.

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Diabetes is related to different pathological states in the oral cavity including premalignant and malignant lesions (1–3). Leukoplakia is an asymptomatic, potentially malignant lesion in the oral mucosa. Between <1 and 18% of oral premalignant lesions will develop into oral cancer (4). Smoking and drinking alcohol are main risk factors for this disease (5). Even though there is a strong association between diabetes and leukoplakia, a causal mechanism for that has not been elucidated. In the present study, we assess the effect of metabolic risk factors on oral leukoplakia.

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significant interaction with current smoking (95% CI 1.08–2.12), thereby exhibiting leukoplakia, indicating an increase in the risk of oral leukoplakia most pronounced in nonsmokers. Smoking seems to override the metabolic impact. The smoke-related burden is high even at low levels of A1C or LDL-C. Chronic metabolic deteriorations may have a similar influence on the risk as lifetime exposure to tobacco smoking expressed as pack-years.

Results from the logistic regression suggest that there is a continuously increasing risk with increasing levels of A1C or of LDL-C. Accordingly, the risk seems to be related to quantitative metabolic disturbances rather than to distinct cases of diabetes. As in other tissues, the diabetic metabolism leads to profound deteriorations in the oral cavity that may predispose for oral leukoplakia (9). The association of leukoplakia with increasing LDL-C/HDL-C ratios could be explained by the disturbed lipid metabolism frequently seen in diabetic patients (10). Premalignant lesions are often associated with a background of chronic inflammation (11).

Diabetes is one of the main risk factors, besides smoking, of inflammatory periodontitis (12). The dental parameters (Table 1) indicate a possible role of local inflammation and may be related to the risks in common with diabetes (13).

Limitations of this survey are the missing biopsies for diagnosing the oral lesions and nonfasting blood analyses. Lesions were classified as clinical diagnoses, as recommended when biopsies are missing (14). The cross-sectional study design precludes causal considerations.

The results fit the hypothesis that accumulation of carbohydrates contributes to the risk of preneoplastic lesions (15). Metabolic disturbances in diabetes with interactions between systemic and local factors have manifestations in the oral cavity.

| Table 1—Characteristics of participants included in the matched-pair analysis with leukoplakia (n = 123) and control subjects without (n = 246), matched for age and sex |
|---------------------------------|----------------|----------------|------|
|                                  | Leukoplakia    | No leukoplakia  | P    |
| Subjects (female/male) (n)      | 55/68          | 110/136         | §    |
| Age (years)                     | 55.2 ± 15.5    | 55.2 ± 15.6     | §    |
| Smokers                         |                |                |      |
| Former (%)                      | 25 (20)        | 55 (22)        | 0.389|
| Current (%)                     | 50 (41)        | 55 (22)        | <0.001|
| Pack-years smoked               | 13.8 ± 21.1    | 8.5 ± 14.3     | 0.002|
| Alcohol (g/week)                | 106 ± 154      | 82 ± 115       | 0.472|
| Subjects with type 2 diabetes (%)| 27 (22)        | 31 (13)        | <0.001|
| A1C (%)                         | 6.0 ± 1.2      | 5.6 ± 1.0      | 0.002|
| Glucose (mmol/l)*               | 6.5 ± 2.6      | 5.8 ± 1.7      | 0.007|
| Total cholesterol (mmol/l)*     | 6.2 ± 1.3      | 5.7 ± 1.2      | 0.003|
| LDL/HDL cholesterol ratio       | 3.1 ± 1.3      | 2.6 ± 1.0      | 0.004|
| LDL-C (mmol/l)*                 | 3.9 ± 1.2      | 3.5 ± 1.1      | 0.008|
| HDL-C (mmol/l)*                 | 1.4 ± 0.4      | 1.5 ± 0.4      | 0.194|
| WBC count (Tpt/l)               | 7.1 ± 2.1      | 6.6 ± 1.9      | 0.087|
| hs-CRP (mg/l)                   | 3.4 ± 4.7      | 3.0 ± 6.0      | 0.225|
| Fibrinogen (mg/l)               | 3.1 ± 0.7      | 3.0 ± 0.7      | 0.072|
| Subjects with visceral obesity (%)†| 47 (38)       | 68 (28)       | 0.039|
| Subjects with hypertension (%)† | 53 (43)        | 97 (39)        | 0.500|
| Education ≥10th grade (%)       | 53 (43)        | 121 (49)       | 0.269|
| Last dental visit >1 year back (%) | 34 (28)   | 45 (18)       | <0.001|
| Mean gingival attachment loss (mm) | 3.6 ± 2.2  | 2.9 ± 2.0     | 0.012|
| Attachment loss, % of sites ≥3 (mm) | 75 (33–97) | 49 (19–89)   | 0.027|
| Gingival bleeding on probing, % of sites | 46 (25–75) | 35 (12–58)  | 0.010|
| Edentulous subjects (%)         | 26 (21)        | 41 (17)        | 0.294|

Data are means ± SD, n (%) median (interquartile range). WBC, white blood cell. †Matching variable. §Never smokers, *nonfasting. †According to National Cholesterol Education Program, Adult Treatment Panel III.

CONCLUSIONS — Smoking and drinking alcohol have long been regarded as the sole cause in the etiology of premalignant oral mucosa lesions such as leukoplakia (5). However, in the search for further risk factors, diabetes may also be associated with the occurrence of oral leukoplakias as well. In large population studies, diabetic individuals have been reported to be over-represented in subjects with oral lesions. In the National Health and Nutrition Examination Survey III, an OR of ~2 was found, suggesting that diabetes is a strong predictor of oral leukoplakia (4). Similar figures were reported in a study including more than 900 leukoplakia cases in women but not in men (3). We found evidence that diabetes-related metabolic factors are associated with the occurrence of leukoplakia most pronounced in nonsmokers. Smoking seems to override the metabolic impact. The smoke-related burden is high even at low levels of A1C or LDL-C. Chronic metabolic deteriorations may have a similar influence on the risk as lifetime exposure to tobacco smoking expressed as pack-years.

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