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.

RESEARCH DESIGN AND METHODS

— The Study of Health in Pomerania (SHIP) is a cross-sectional survey of the adult population in northeast Germany. A random sample was drawn from residents' registration offices and stratified by sex and age (20–80 years). Of the eligible individuals, 68.8% ($n = 4,310$) participated in this study, and 4,210 of them were screened for oral mucosal lesions (6). All participants gave written informed consent. The study was approved by the local ethics committee. Interviews were used to gain information on anamnestic, behavioral, and sociodemographic characteristics. Smoking status was assessed by self-report.

The examination of oral mucosa for lesions, oral leukoplakia, erythroplakia, lichen ruber, ulcers, and others covered all areas of the oral cavity, including the tongue and lips, and was conducted according to the guidelines of the German Cancer Association (7). Examiners were trained for consistent diagnostics with suitable patients and photographic material.

Glycosylated hemoglobin (A1C), total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), plasma fibrinogen (using the Clauss method), and white blood cell count were assayed with standard laboratory methods, and high-sensitivity C-reactive protein (hs-CRP) was assayed by immuno-nephelometry (Dade Behring, Inc.). For A1C levels, a threshold of ≥6.5% was set (8).

A total of 123 case subjects with leukoplakia simplex were identified and a 123:246 case-control study was built, matched for sex and age. We used the Mann-Whitney *U* test and contingence tables for continuous and categorical variables, respectively. Leukoplakia was the dichotomous dependent variable in conditional logistic regression and was adjusted for matching variables and potential confounders. Data analyses were performed using STATA.

RESULTS

— Among the study population, 2.9% ($n = 123$) of the patients had oral leukoplakia. These subjects were compared with their unaffected, matched counterparts with respect to general characteristics and clinical chemistry parameters (Table 1). We found significant differences in metabolic parameters characterizing the glucose and cholesterol metabolism. Correspondingly, among the leukoplakia cases, more subjects with type 2 diabetes were noticed. As expected, smoking was over-represented in the cases group. Markers of systemic inflammation (hs-CRP, fibrinogen) were higher in case subjects, and measures re-

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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, ‖reference: never smokers, *nonfasting, †according to National Cholesterol Education Program, Adult Treatment Panel III.

lated to local oral inflammation, such as bleeding or attachment loss, were worse in cases.

In a first stratification for combined risks, we found the crude risk of leukoplakia was increased in never smokers with hyperglycemia of A1C ≥6.5% (OR 2.49 [95% CI 1.05–5.89]) comparable to the risk of normoglycemic smokers (2.21 [95% CI 1.30–3.75]). For those who have both factors combined, the risk of belonging to the leukoplakia group may be even higher (2.66 [95% CI 1.01–6.95]).

A conditional logistic regression was performed adjusting for age, former and current smoking, alcohol consumption, education, and LDL and HDL cholesterol. A1C was significantly associated with leukoplakia, indicating an increase in the probability of the outcome: A1C OR 1.51 (95% CI 1.08–2.12), thereby exhibiting significant interaction with current smoking (A1C × smoking, $P = 0.012$). In nonsmokers, the leukoplakia probability was low at normoglycemic state. But there was a more pronounced increase in the probability of having leukoplakia with the increasing metabolic factor A1C as compared with smokers. Smokers were at increased risk even when having low A1C levels. This was confirmed in an analysis stratified by smoking, resulting in odds ratios associated with A1C: never smokers OR = 1.96 (95% CI 1.15–3.37), ever smokers OR = 1.29 (95% CI 0.80–2.09). Similarly, LDL-C proved to be a risk factor: in never smokers OR = 3.01 (95% CI 1.40–6.50), ever smokers OR = 1.47 (95% CI 1.00–2.15).

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.

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.

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