Retinal and Gingival Hemorrhaging and Chronic Hyperglycemia

Short title: Retinal and Gingival Hemorrhaging

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Submitted 13 May 2010 and accepted 30 September 2010.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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Objective: To assess the hypothesis that retinopathies are indicative of systemic microvascular injury.

Research Design and Methods: The only US national survey assessing microvascular hemorrhaging at two distinct anatomical sites was the National Health and Nutrition Examination Survey (1988-1994). The systemic microvascular injury hypothesis was assessed by modeling the association of retinal and gingival hemorrhaging and the factors that explain this association.

Results: Individuals in whom 1 in 5 gingival sites were hemorrhaging had a 57% increased odds for retinal hemorrhaging (95% confidence interval: 1.26-1.94). This association between retinal and gingival hemorrhaging was for 51% explained by HbA1C concentrations. Retinal and gingival hemorrhaging exhibited the signature J-shaped prevalence patterns when plotted as a function of HbA1C concentrations.

Conclusions: Gingival hemorrhaging reflected on retinal hemorrhaging and both shared chronic hyperglycemia as an explanatory marker. These epidemiological findings support the hypothesis that retinopathies are reflective of systemic microvascular injury.

The retina was often considered the only tissue where microangiopathic processes can be visualized and graded using simple non-invasive diagnostic tools. Studies reported that these retinal pathologies were predictive of systemic morbidities such as myocardial infarction, dementia, stroke, and kidney failure (1). As early as 1988, such findings have led to the hypothesis that retinal microvascular changes are reflective of systemic microvascular injury present in tissues ranging from the kidney to the heart (2). This study’s aim was to assess whether multiple microvascular pathologies can be linked epidemiologically and to explore factors explaining such co-occurrence.

MATERIALS AND METHODS
The Third National Health and Nutrition Examination Surveys (NHANES) was the only national survey in the United States that clinically assessed hemorrhaging at the retina and the dental gingiva (http://www.cdc.gov/nchs/nhanes/nh3data.htm). Retinal hemorrhages or microaneurysms and gingival hemorrhaging were related to each other and to risk factors using generalized estimating equation models with a logit link and a binomial error. The point where the prevalence of retinopathy, retinal hemorrhaging, and gingival hemorrhaging changed as a function of HbA1C was estimated using a joinpoint regression model. The statistical methods for surrogate endpoint evaluation were employed to explore which markers explained the association between gingival and retinal hemorrhaging (3). The proportion explained of the retinal-gingival hemorrhaging association was estimated as $(\beta - \beta_s)/\beta$, where $\beta$ and $\beta_s$ are estimates of the effect of gingival hemorrhaging on retinal hemorrhaging with and without adjustment for...
suspected markers of systemic microvascular injury (4). If adjustment for a marker changed the predictive effect of gingival hemorrhaging on retinal hemorrhaging from statistical significance (p-level < 0.05) to non-significance (p > 0.05), the marker was considered valid following the Prentice criterion (5).

RESULTS
Gingival and retinal hemorrhaging were predictive of each other. The presence of gingival hemorrhaging at more than 5% or 20% of the periodontal sites increased the odds for retinal hemorrhaging by 38% (odds ratio, 1.38; 95% confidence interval: 1.12-1.68) and 57% (odds ratio, 1.57; 95% confidence interval: 1.26-1.93), respectively. Several risk factors were consistently associated both retinal and gingival bleeding. Increasing age (p < 0.001), Mexican-American heritage (p < 0.05), and poverty (p < 0.001) were associated with an increased prevalence of both retinal and gingival hemorrhaging. Similarly, high systolic blood pressure (p < 0.001), increasing levels of triglycerides (p < 0.001), larger waist circumference (p < 0.001), decreasing levels of high-density lipoproteins (p <0.002), increasing levels of hemoglobin A1c levels (p <0.0001), C-reactive protein (p <0.001), and serum insulin levels (p <0.001) were associated with an increased prevalence of both retinal and gingival hemorrhaging. Decreasing serum vitamin D (p < 0.001) and C levels (p< 0.05) were associated with an increase in both retinal and gingival hemorrhaging. Finally, increasing serum cotinine levels was associated with both decreased gingival and retinal hemorrhaging (p < 0.05).

Of all these risk factors which had similar impacts on gingival and retinal bleeding, only HbA1c level satisfied the Prentice criterion a valid marker. HbA1c explained 51% of the systemic microvascular injury. None of the other risk factors when evaluated independently or in conjunction were valid markers of the systemic microvascular injury according to the Prentice criteria.

The prevalence of gingival hemorrhaging, retinal hemorrhaging, and retinopathies was plotted as a function of the deciles of hemoglobin A1c levels (Figure 1 and Supplementary Figure in the online appendix available at http://care.diabetesjournals.org). The HbA1c change points for gingival hemorrhaging, retinal hemorrhaging, and retinopathies were at 6.1% (95% confidence interval, 5.9-6.6), 5.9% (95% confidence interval, 5.7-6.3), and 6.0% (95% confidence interval: 5.8-6.3) respectively. The gingival hemorrhaging, the retinal hemorrhaging and the retinopathy prevalence were highly correlated (pairwise correlation coefficients > 0.99, p < 0.0001).

DISCUSSION
This study documented that individuals with gingival hemorrhaging are more likely to have retinal hemorrhaging and vice-versa. This finding is in and of itself not new. Case reports have indicated that gingival hemorrhaging can be reflective of systemic microvascular pathology for scurvy (6), hemorrhagic fever (7), leukemia (8), vitamin K deficiency (9) and von Willebrand disease (10). What is novel about the reported findings is that the co-occurrence of retinal and gingival hemorrhaging was verified at a population level and that about 50 percent of the association was explained by one of the most common metabolic disorders – abnormal glucose metabolism (11). These findings hereby provide direct epidemiological evidence in support of the 1988 hypothesis that
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Retinal hemorrhaging is a marker of systemic microvascular injury(2). Chronic hyperglycemia was the dominant marker explaining approximately fifty percent of the association between gingival and retinal hemorrhaging. Several lines of evidence suggest that chronic hyperglycemia may be reflective of an underlying causal mechanism - possibly unrelated to chronic hyperglycemia per se - driving both retinal and gingival hemorrhaging. First, both gingival and retinal hemorrhaging had the same hockey-stick prevalence pattern when plotted as a function of chronic hyperglycemia. This suggests that both the gingival and retinal microvasculature undergo pathological changes around the same critical points of glycation. Second, individuals with gingival hemorrhaging – just like individuals with retinal hemorrhaging - are more likely to be diabetic or to express markers of diabetes (12; 13). And third, the microvascular pathologies of gingivitis and retinopathies are similar histologically; both are described as microvascular angiopathies with edema, vascular proliferation and tortuosity, hemorrhaging, membrane thickening(14). It is also possible that the bleeding at both sites is caused by diabetes rather than by the glycemia per se. These different lines of evidence suggest that abnormal carbohydrate metabolism may be an important marker explaining why retinal and gingival hemorrhaging co-occur in individuals of a typical western population.

In summary, these findings are consistent with the 1988 hypothesis that retinopathies are reflective of hidden systemic microvascular injuries that are largely driven by abnormal glucose metabolism. Further research on the pathologies associated with systemic microangiopathic processes could harness power by evaluating consistency of patterns across multiple microvascular systems. Until the diagnostic technology improves for assessing microvasculatures at sites such as the brain or the myocardium, gingival tissues could offer a easily accessible anatomical site to further study systemic microangiopathic processes.

**Author contributions:** Philippe Hujoel wrote the manuscript and performed all statistical analyses except the joinpoint regression. Marni Stott-Miller edited the manuscript, did the joinpoint regression, and checked the statistical analyses. No editorial assistance was received.

**ACKNOWLEDGMENTS**
We would like to thank Dr. Eugenio Beltrán-Aguilar for discussions of this project and dental issues related to NHANES data. (Centers for Disease Control and Prevention Division of Oral Health Mail Stop F-10 4770 Buford Highway NE Atlanta, GA 30341)

**Disclosure.** No financial conflict of interest to declare.

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**Figure Legend**
**Figure 1.** Prevalence of gingival hemorrhaging, retinal hemorrhaging and retinopathies as a function of Hemoglobin A1C levels
REFERENCES
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Figure

![Graphs showing the prevalence of retinal and gingival hemorrhaging with respect to hemoglobin levels in various deciles.](image)

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