Retinal and Gingival Hemorrhaging and Chronic Hyperglycemia

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OBJECTIVE — To assess the hypothesis that retinopathies are indicative of systemic microvascular injury.

RESEARCH DESIGN AND METHODS — The only U.S. 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 one or more in five gingival sites was hemorrhaging had a 57% increased odds for retinal hemorrhaging (95% CI: 1.26–1.94). This association between retinal and gingival hemorrhaging was 51% explained by A1C concentrations. Retinal and gingival hemorrhaging exhibited the signature J-shaped prevalence patterns when plotted as a function of A1C 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.

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The retina was often considered the only tissue in which microangiopathic processes can be visualized and graded using simple noninvasive diagnostic tools. Studies reported that these retinal pathological conditions 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). The aim of this study was to assess whether multiple microvascular pathological conditions can be linked epidemiologically and to explore factors explaining such co-occurrence.

RESEARCH DESIGN AND METHODS

— The Third National Health and Nutrition Examination Survey (NHANES) was the only national survey in the U.S. that clinically assessed hemorrhaging in 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 at which the prevalence of retinopathy, retinal hemorrhaging, and gingival hemorrhaging changed as a function of A1C was estimated using a joinpoint regression model. The statistical methods for surrogate end point evaluation were used to explore which markers explained the association between gingival and retinal hemorrhaging (3). The proportion of the retinal-gingival hemorrhaging association that was explained was estimated as $(\beta - \beta_s)/\beta$, where β and β_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 ($P < 0.05$) to nonsignificance ($P > 0.05$), 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 ≥20% of the periodontal sites increased the odds for retinal hemorrhaging by 38% (odds ratio 1.38 [95% CI 1.12–1.68]) and 57% (1.57 [95% CI 1.26–1.93]), respectively. Several risk factors were consistently associated with 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 HDL ($P < 0.002$), and increasing A1C ($P < 0.0001$), 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 ($P < 0.05$) levels were associated with an increase in both retinal and gingival hemorrhaging. Finally, increasing serum cotinine levels were associated with both decreased gingival and retinal hemorrhaging ($P < 0.05$).

Of all the risk factors that had similar impacts on gingival and retinal bleeding, only A1C level satisfied the Prentice criterion as a valid marker. A1C 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 criterion.

The prevalence of gingival hemorrhaging, retinal hemorrhaging, and retinopathies is plotted as a function of the deciles of A1C levels (Fig. 1 and supplementary Figure 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0901/DC1). The A1C change

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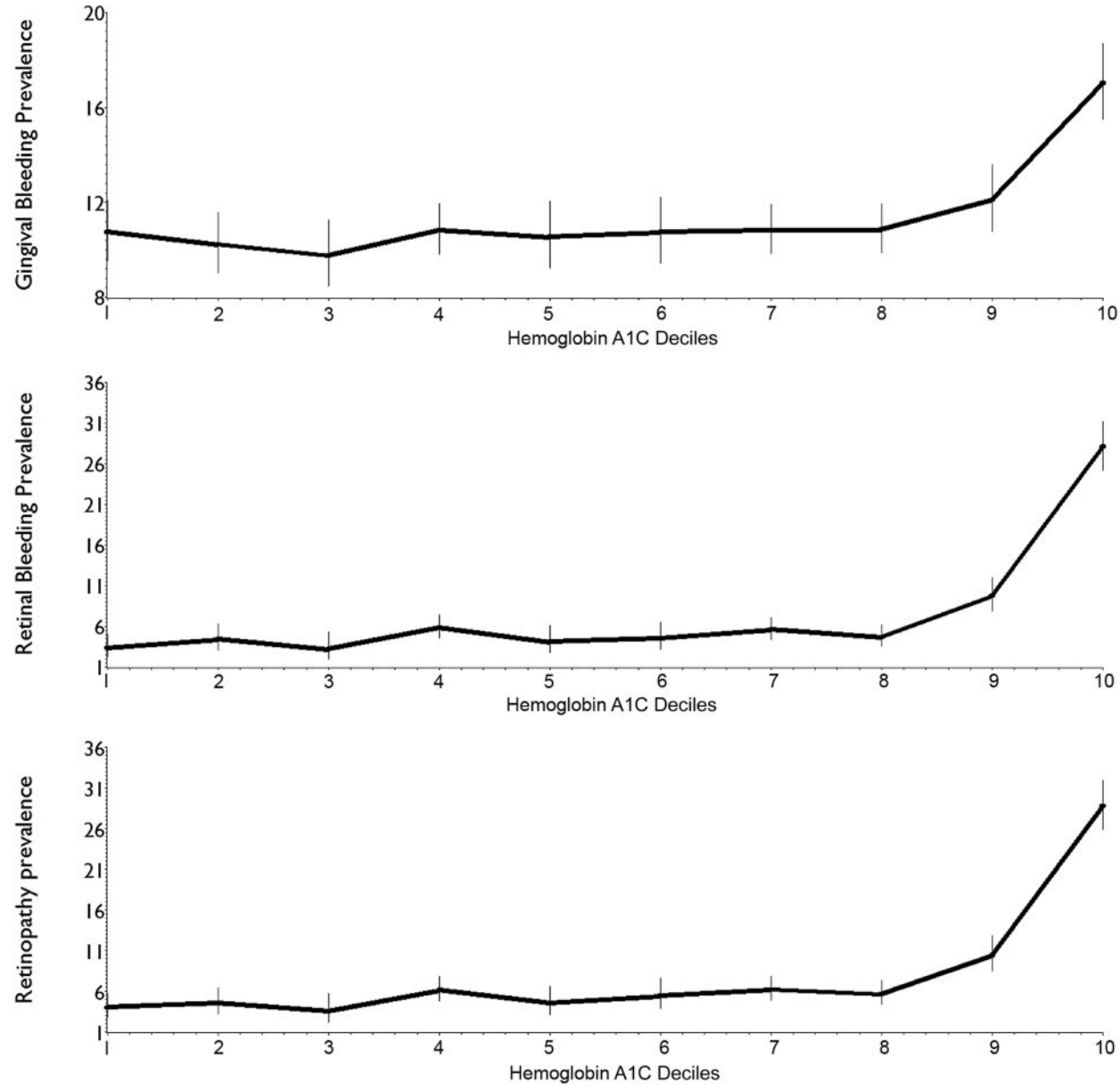

Max	4.8	5.0	5.1	5.2	5.3	5.5	5.7	5.9	6.6	16.1
Mean	4.6	5.0	5.1	5.3	5.4	5.5	5.6	5.9	6.3	8.7
Min	3.3	5.0	5.1	5.2	5.4	5.5	5.6	5.8	6.1	6.7

Figure 1—*Prevalence of gingival hemorrhaging, retinal hemorrhaging, and retinopathies as a function of A1C levels. Max, maximum; Min, minimum.*

points for gingival hemorrhaging, retinal hemorrhaging, and retinopathies were at 6.1% (95% CI 5.9–6.6), 5.9% (5.7–6.3), and 6.0% (5.8–6.3), respectively. The gingival hemorrhaging, the retinal hemorrhaging, and the retinopathy prevalence were highly correlated (pairwise correlation coefficients >0.99, $P < 0.0001$).

CONCLUSIONS — This study documented that individuals with gingival hemorrhaging are more likely to have retinal hemorrhaging and vice versa. This finding is 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 ~50% 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 retinal hemorrhaging is a marker of systemic microvascular injury (2).

Chronic hyperglycemia was the dominant marker explaining approximately 50% 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, that is 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 finding 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 pathological conditions of gingivitis and retinopathies are similar histologically; both are described as microvascular angiopathies with edema, vascular proliferation and tortuosity, hemorrhaging, and 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 pathological conditions associated with systemic microangiopathic processes could harness power by evaluating consistency of patterns across multiple microvascular systems. Until the diagnostic technology for assessing microvasculatures at sites such as the brain or the myocardium improves, gingival tissues could offer an easily accessible anatomical site to further study systemic microangiopathic processes.

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P.H. performed all statistical analyses except the joinpoint regression and wrote the manuscript. M.S.-M. performed the joinpoint regression, checked the statistical analyses, and revised/edited the manuscript.

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