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Risk indicators for recurrent aphthous ulcers among adults in the US

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Abstract – *Background and aims:* Recurrent aphthous ulcers (RAU) in the oral cavity are painful, causing substantial morbidity in the US and elsewhere in the world. Despite this, there is a lack of population-based studies representative of the US national adult population to describe the epidemiology, and estimate the true disease burden and association with independent risk factors. Although several studies have investigated the role of various factors in RAU etiology, the epidemiology and etiology of RAU remain unclear. This study aims to establish the prevalence and describe the epidemiology of RAU in adults. *Methods:* Data from the Third National Health and Nutrition Examination Survey (NHANES III) were analyzed in SUDAAN using multivariable logistic regression, modeling RAU occurrences. *Results:* Overall, for all Americans regardless of age, prevalence of RAU was 1030 per 100 000 people (95% CI 830–1220). The prevalence of RAU among adults was 850 per 100 000 (95% CI 630–1070). The lower vestibule was the most commonly involved site. Multivariable analyses suggested that adjusted odds of RAU were greatest for those 17–29 years of age (adjusted OR 2.7; 95% CI 1.4–5.5), for men (adjusted OR 1.7; 95% CI 0.9–2.8), and for those with low serum insulin levels (OR 2.0; 95% CI 0.9–4.4). Never smokers had greater risk of RAU (OR 9.2, 95% CI 2.8–30.1) compared with those who smoked more than 10 cigarettes per day. *Conclusion:* This study establishes the prevalence of RAU among adults in the US and demonstrates that whereas cigarette smoking is associated with lesser odds, low insulin levels might be independently associated with greater odds of RAU.

Key words: epidemiology; oral mucosal oral pathology; recurrent aphthous ulcer

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Among the most commonly cited studies for recurrent aphthous ulcer (RAU) prevalence (1–9), only three are population-based studies (1, 2, 5) of which the only one carried out in the US (5) was for schoolchildren based on the National Institute of Dental and Craniofacial Research (NIDCR) National Survey of Oral Health in US School Children (1986–1987). Studies on RAU are published frequently, but a high proportion of those are reviews. We conducted a Medline search of all articles published between January 1, 1999 and August 24, 2004 with 'aphthous ulcer' as the key word. This returned 297 articles of which 64 (21.55%) were marked as reviews – among these, 22 (34.4% of reviews and 7.4% overall) had 'aphthous ulcer' named in the title of the article. All reports have pointed out the poor evidence and understanding about the etiology of RAU (6, 10). Although a recent study (11) has reported the association of adult RAU with a host of factors, the study failed to include smaller race–ethnicity groups which formed 8% of the sample. Furthermore, multivariable models described in the study did not include some biochemical factors that we consider are important in RAU etiology.

Independent risk factors of RAU have not been clearly established in population-based studies, and most evidence comes from convenience samples and clinic-based studies. Prevalence of RAU has been reported to vary between 1% and 66% among adults (6, 11) and 1% and 40% among children (5, 6, 10). RAU may present as major, minor or herpetiform mucosal ulcers in the oral cavity (6). The suggested association of RAU with different factors include genetic (11), negative association with smoking (8, 9, 12, 13, 14), oral contraceptives (10), cyclical association with menstrual cycle stage (9), positive association with T-cell-mediated immune responses (15–17), tumor necrosis factor (TNF)-α (18), interleukin (19), keratinocyte maturity (7), heat shock proteins (20), hematinic deficiencies such as vitamins B1 B2 and B6 (7), folate deficiency (21), zinc deficiency (22), and defective mucosal epithelial turnover (9). Oral streptococci were suggested as important determinants of RAU either as direct pathogens or as an antigenic stimulus culminating in the genesis of antibodies that may cross-react with keratinocyte antigenic determinants (23). but this was later refuted (24). Similarly, *Mycobacterium tuberculosis* (25), *Helicobacter pylori* (26, 27), herpes viruses (28–30), varicella zoster virus (31), and cytomegalovirus (32, 33) have been implicated in RAU.

Poor understanding of RAU etiology has also spawned a variety of possible treatment regimens proposed through clinical case series and clinical trials without strong evidence to support or refute efficacy or effectiveness of any. Suggested treatment modalities have aimed at symptomatic relief or at effecting a biological cure with no clear indication of superiority of either with no available specific treatment for RAU (10, 34, 35). The goals of treatment of RAU have been to include control of pain, promotion of healing, and decreased numbers of future ulcers (35).

This report aims to establish the prevalence of RAU in adults through a population-based study. This is the first step before etiological parameters can be examined in detail to establish, support or refute various hypotheses. This is the first study using a large set of data that allow generalizable robust multivariable analyses. The specific aims of this study were to: (a) establish the prevalence of aphthous ulcers in the adult US population by determining population estimates, and (b) develop an explanatory model of factors associated with RAU that is generalizable to the US population.

Methods

This study used the Third National Health and Nutrition Examination Survey (NHANES III) data available from the National Center for Health Statistics (NCHS) website of Centers of Disease Control (CDC). NHANES III was conducted by the NCHS of the CDC from 1988 to 1994 for investigating risk factors that may explain racial and ethnic differences in health and nutrition information on the US civilian non-institutionalized population (36). NHANES III was the seventh in a series of national examination surveys in the US conducted on a complex random sample of households in 81 counties. NHANES III consisted of two phases of equal length, each comprising a random sample of the US population living in households, and was oversampled on African–Americans, on Hispanics, on children aged 2 months to 5 years, and on persons aged 60 years and more. NHANES III used a stratified, multistage, probability design in which 13 944 youths aged 2 months to 16 years and 20 050 adults aged 17+ years were interviewed and underwent a direct physical examination. Dental examinations were conducted on all subjects aged 13 years and more.

Persons aged 2 months and more were asked to participate in an extensive interview and examination in a large mobile examination center (MEC). NHANES III contained a number of health status components, including oral health. The main element in the oral health component was an oral examination conducted in the MEC. During the MEC examination, the dentist performed complete oral examinations of all persons aged 12 months and more, and oral soft-tissue examinations on all persons aged 2 months and more. The complete examination contained visual assessment of the oral mucosa, laboratory assessment of an oral smear for *Candida albicans*, coronal caries (≥12 months), root caries (≥18 years), history of injury to anterior teeth, occlusal assessment (aged 8–50 years), and a periodontal examination using the NIDCR protocol on two randomly selected quadrants of the mouth (aged 13 years or more). Restorations and tooth conditions for persons aged 18–74 years were also assessed. The household adult questionnaire, administered to adults aged 17 years or more, included questions on use of dental health services and on risk factors and health behaviors associated with many chronic diseases. RAU was diagnosed when the following case definition criteria were met: lesions were

painful, well-defined grayish-white ulcers surrounded by red halo, usually found on non-keratinized surfaces that lasted for 10–21 days with a history of recurrence (36). The study participants were probed for past history and duration in order to justify the clinical diagnosis.

Statistical analyses

This project, using data from NHANES III, has a cross-sectional design, and was analyzed using RAU occurrence as a dichotomous categorical outcome variable; and sociodemographic, blood biochemistry, and microbial antibody titers were included as independent variables. Covariates included age categories, gender, race/ethnicity (non-Hispanic White, non-Hispanic Blacks, Mexican–Americans, and others), and level of education [11 years or less of education (less than high school), 12 years (high school), and more than 12 years (more than high school, the reference group)]. Family income was categorized as: less than 20 000 (20 K), 20–50 K, greater than 50 K dollars per annum; and 'unknown/unreported' groups. We retained the 'others' group in the race/ethnicity variable and 'unknown' in income groups in the analyses because of their substantial numbers and distinctly greater prevalence of RAU in these subgroups. Portions of the oral examination of particular relevance to the present study included the assessment of the oral mucosa for mucosal lesions using the NIDCR protocol and WHO diagnostic criteria (36). The outcome variable, RAU was derived from the oral mucosal examination section of the data. We categorized biochemical variables such as serum iron, serum folate and others according to their clinical 'normal range into being low' or 'normal-high'. To establish stable cell sizes for meaningful analyses, we dichotomized serum insulin level at 8 μU/mL so that values <8 μU/mL were classified as low serum insulin. We examined cigarette smoking in two ways. First we examined the differences between never smokers and ever smokers defined as those who had smoked at least 100 cigarettes in their lifetime. Thereafter, we categorized smoking into a three-level variable to obtain stable cell sizes for analyses: never smokers; those who smoked less than 10 cigarettes per day; and those who smoked 10 or more cigarettes per day.

We merged all relevant variables from the 'EXAM' and 'ADULT' data files by their unique identifier 'SEQN'. For inclusion in this study, the person had to be identified in both the files, and had to have a record of dental examination. The data were structured so that one observation represented one person – the unit of analysis. Valid, although extreme out-of-range values were re-coded to the highest reasonable value (usually 99th percentile data value) to avoid influence of very few unusually extreme values on the mean. The data were summarized using frequencies and mean values. Univariate analyses and bivariate associations were determined using differences between mean values, odds ratios (OR) and 95% confidence intervals (CIs). Odds ratios different from unity were considered as preliminary evidence of the covariate as a confounder if it was also found to be associated both with the exposure and outcome. Continuous variables were then categorized based on frequency distributions, and stratified analyses were performed (i.e. the main exposure–outcome associations were stratified by each covariate).

We assessed the probability of having RAU was assessed by logistic regression after adjusting for the complex sample design. The independent variables included: age, sex, smoking, race/ethnicity, geographical region, rural/urban location, education, family income, clinical depression, serum cobalamine (vitamin B12), serum iron, serum folate and serum insulin levels, serum Herpes Simplex Virus (HSV)-1 and serum HSV-2 antibody level, and serum *H. pylori* antibody level. We undertook modeling to develop explanatory models of the relationship between exposures and outcome. All continuous and ordinal variables were assessed for linearity in the logit. Analyses used main-effect multivariable models fit using logistic regression. Covariates in the model were specified *a priori* and were assessed for usefulness using likelihood ratio tests for hierarchically well-formulated models to arrive at the most parsimonious and plausible explanatory model. To develop the explanatory model, a 'full' model was defined with all relevant variables in it. A manual backward elimination process employing the likelihood test was used to reach the most parsimonious final explanatory model for RAU. All data were analyzed in SAS (V8.2, SAS Institute, Cary, NC, USA) and SUDAAN (37) using appropriate weights and variance adjustments accounting for the complex sample design.

Results

Overall, for all Americans regardless of age, this study found RAU prevalence to be 1030 per

100 000 persons (95% CI: 830–1220). The prevalence of RAU among children was 1500 per 100 000 (95% CI 1090–1910) and was greater than that among adults at 850 per 100 000 (95% CI 630–1070). Compared with the national average prevalence, statistically significantly lesser RAU prevalence was noted among non-Hispanic Blacks, whereas prevalence among 17- to 29-year-old adults was significantly higher (Table 1). Prevalence was substantially greater than the national average (although not statistically significantly at the 0.05 level) for males; those with unknown annual family income; those living in West region; Mexican–American and other race/ethnic groups that included Hispanics not included elsewhere (Table 1). RAU prevalence among those who had ever smoked (570/100 000) was about half of that among never smokers (1170/100 000). Furthermore, compared with never smokers, RAU prevalence among those who smoked 10 or more cigarettes per day was about 10 times lower (120/100 000).

Table 1. Prevalence of RAU among adults in the US (NHANES III)

Characteristic	Level	Prevalence, % (95% CI)
Demographic characteristic		
Overall	<1 to ≥60 years	1.03 (0.83–1.22)
Children/adolescents	<1 to <19 years	1.5 (1.09–1.91)
Adults	17 to ≥60 years	0.85 (0.63–1.07)
Age	17–29 years	1.44 (0.85–2.03)
	30–39 years	0.85 (0.42–1.28)
	40–49 years	0.52 (0.13–0.91)
	50–59 years	0.52 (0.13–0.91)
	≥60 years	0.59 (0.32–0.86)
Sex	Male	1.09 (0.72–1.46)
	Female	0.64 (0.42–0.86)
Annual family income	<20 K	0.73 (0.42–1.04)
	20–50 K	0.94 (0.59–1.29)
	50 K+	0.75 (0.30–1.20)
	Unknown	1.19 (0.09–2.29)
Census tract region	Northeast	0.61 (0.22–1.00)
	Midwest	0.82 (0.41–1.23)
	South	0.86 (0.51–1.21)
	West	1.11 (0.56–1.66)
Rural/urban	MSA	0.91 (0.62–1.20)
	Non-MSA	0.8 (0.51–1.09)
Race/ethnicity	Non-Hispanic White	0.86 (0.61–1.11)
	Non-Hispanic Black	0.39 (0.21–0.57)
	Mexican–American	1.11 (0.80–1.42)
	Others	1.26 (0.24–2.28)
Cigarette smoking	Ever	0.57 (0.81–0.33)
	Never	1.17 (0.8–1.5)
	10 or less per day	1.37 (0.3–2.4)
	More than 10 per day	0.12 (0.01–0.26)
Years of education	Less than high school	0.77 (0.44–1.10)
	High school	0.93 (0.54–1.32)
	More than high school	0.85 (0.50–1.20)

Mean age of those with RAU (36.1 years, SE 1.92) was significantly lesser than those without RAU (mean 43.3 years, SE: 0.43; *t*-test: $P = 0.003$). Mean age for those with single lesion (30.9 years, SE 1.9) was lower, though not significantly from those with multiple lesions (mean 39.2, SE 2.0). Among those with RAU, though statistically not significant, fewer people lived in the Northeast whereas more lived in the West. Similarly, non-Hispanic Blacks formed a smaller proportion with RAU whereas the other race/ethnic group (includes non-Mexican American Hispanics) contributed a larger proportion to RAU occurrences. Those in the 17–29 year age group contributed a larger share to RAU occurrences (overall chi-squared, $P = 0.05$) and there seems to be a reversal in trend around 30–39 years after which fewer people report RAU. More men than women reported RAU.

Some 8% people had RAU in multiple sites within the oral cavity; 18% on the left side, 26% on the right, whereas 50% occurred in front (such as labial mucosa), or midline structures (such as palate, dorsum/venter of the tongue, or floor of the mouth). Figure 1 describes site-wise occurrences in more detail. Although the literature describes association of several oral mucosal co-morbidities with RAU, such as acute necrotizing gingivitis, amalgam tattoo, cheek/lip bite, denture stomatitis, denture ulcer, frictional white lesion, herpes labialis, nevus, fissured tongue, geographic tongue, and other lesions such as scar/surgical scar, hemangioma, denture inflammation and fistula, we did not find any significant association of RAU with these co-morbidities.

Risk of RAU was similar for those who reported having suffered symptoms of clinical depression (both for 1 year and for 2 years) and those not reporting depression. Mean values of serum herpes virus-1 and herpes virus-2 antibodies, serum *H. pylori* antibody, serum iron, serum cobalamine, serum folate, plasma glucose, blood hemoglobin, red cells, and white cells were similar for those with RAU and those without RAU. Mean serum insulin was statistically significantly lower ($P = 0.0004$) for those with RAU compared with those without RAU.

Multivariable logistic regression analyses (Table 2) suggested that the adjusted odds for RAU were

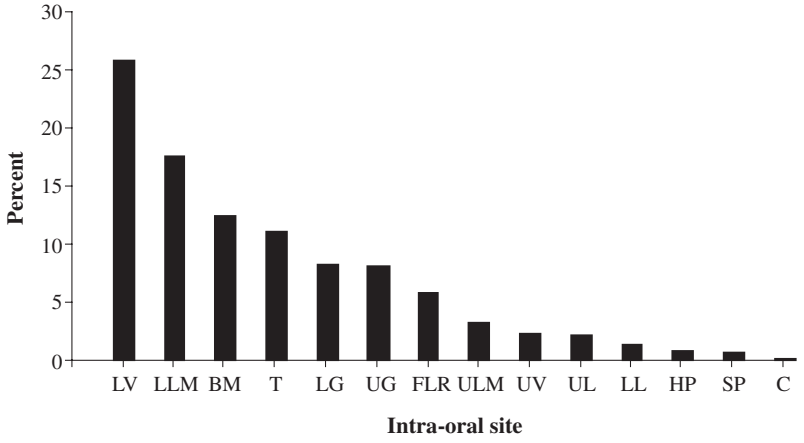

Fig. 1. Distribution of RAU among adults in the US by intra-oral site (NHANES III). LV, lower vestibule; LLM, lower labial mucosa; BM, buccal mucosa; T, tongue; LG, lower gingiva; UG, upper gingiva; FLR, floor of the mouth; ULM, upper labial mucosa; UV, upper vestibule; UL, upper lip; LL, lower lip; HP, hard palate; SP, soft palate; C, commisure.

greatest for those 17–29 years of age (adjusted OR 2.7; 95% CI 1.4–5.5); for men (adjusted OR 1.7; 95% CI 0.9–3.3), and among those with low serum insulin levels (OR 2.0; 95% CI 0.9–4.4). Compared with those who smoked more than 10 cigarettes per day, never smokers had greater risk of RAU (OR 9.2; 95% CI 2.8–30.1) (Table 2). Bivariate association with RAU seen for cigar smokers, tobacco chewers and other factors were not apparent upon multivariable adjustment in the fully adjusted model and were not retained in the final model. Upon comparing ORs between crude, fully adjusted and final models, most ORs or their CIs did not change appreciably for any variables because of adjustment.

Table 2. Odds ratios (95% CI) for RAU among adults in the US (NHANES III) from bivariate (crude), and model retaining only significant variables (final model)

Characteristic	Level	Crude	Final model
Age	17–29 years	2.5 (1.3–4.6)	2.7 (1.4–5.5)
	30–39 years	1.5 (0.7–3.0)	2.2 (0.9–5.5)
	40–49 years	0.9 (0.4–2.2)	1.2 (0.4–4.1)
	50–59 years	0.9 (0.4–1.9)	1.7 (0.6–5.0)
	≥60 years	1	1
Sex	Men	1.7 (1.0–2.9)	1.7 (0.9–3.3)
	Women	1	1
Cigarette smoking (per day)	None	10.0 (3.1–32.5)	9.2 (2.8–30.1)
	10 or less	11.8 (1.6–88.0)	10.8 (1.4–84.9)
	More than 10	1	1
Serum insulin	Low	2.1 (1.2–3.9)	2.0 (0.9–4.4)
	Normal or high	1	1
Race/ethnicity	Non-Hispanic White	0.7 (0.4–1.1)	
	Non-Hispanic Black	0.3 (0.2–0.7)	
	Mexican–American	0.9 (0.5–1.6)	
	Others	1	
Census region	Northeast	0.5 (0.2–1.3)	
	Midwest	0.7 (0.4–1.4)	
	South	0.8 (0.4–1.6)	
	West	1	
Rural/urban	MSA	1.1 (0.6–2.1)	
	Non-MSA	1	
Years of education	≥11 years	0.9 (0.5–1.8)	
	12 years	1.1 (0.6–2.0)	
	>12 years	1	
Annual family income	<20 K	0.6 (0.2–1.8)	
	20–50 K	0.8 (0.3–2.2)	
	50 K+	0.6 (0.2–2.2)	
	Unknown	1	

Other variables in the model: mental depression, serum vitamin B12, serum iron, serum folate levels.

Discussion

Several earlier reports have provided varying estimates for prevalence of RAU ranging from 1% to 66% among adults (6, 11) and 1% to 40% among children (5, 6, 10). However, we found a substantially lesser prevalence of RAU (1.03% overall), which when stratified by age suggests 0.85% prevalence among adults and 1.5% prevalence among children and adolescents. Because the NHANES III data were analyzed with appropriate nesting and weighting statements to adjust the variance for the complex sampling design of the survey, these results can be generalized to the US population. Sampling design and selection of study populations seriously impact the conclusion of studies, and convenience samples can provide estimates that may not reflect reality (38). It is likely that most of the earlier reports suggesting higher prevalence of RAU overestimated RAU prevalence because the denominator value used was small and not representative of the population being studied. Using prevalence estimates from this study and based on recent census data (39), there seem to be at least 3 million people having RAU, of which about 2 million are aged 17 years or more, and about 1 million below the age of 17 years. Because RAU has an episodic nature, it is possible that some cases may have been missed during the NHANES examination. This suggests that there it is possible that the true prevalence of RAU may have been underestimated. The prevalence estimates in our study varies somewhat from those presented by another recent study (11) because Rivera-Hidalgo et al. (11) excluded all persons belonging to 'other race categories from their study. Such a practice would reduce the denominator size, and biases prevalence estimates to underestimate prevalence. This idea is strengthened because prevalence of RAU was highest in this heterogeneous 'other' race/ethnic category. Furthermore, the 'other' race/ethnic group also formed about 8% (weighted) of the NHANES III sample included in this study because of which we considered it prudent to include them in the study.

We used NHANES III designated broad annual family income categories for this analysis even though an alternative in Poverty income ratio (PIR) as a continuous variable was available in the data. PIR was created in NHANES to allow income data to be analyzed in a comparable manner across the 6 years of the survey and with previous NHANES. However, in NHANES III a substantial proportion of persons refused to report their income or income category in the family questionnaire (36). As a result of this income non-response, the potential for bias in PIR may be high (36). To minimize potential biases related to income, the broad categorical variable for income was used, keeping the unknown/not reported income as a category in the analyses. Curiously, within the income categories, prevalence of RAU was highest in the unknown/not reported income group. As mentioned earlier for race/ethnic groups, we considered it prudent to include the 'unknown' income group in our analyses rather than ignore this large group of the study sample. Ignoring this large group would have reduced the total number of observations used in multivariable analyses and could have led to inappropriate outcomes.

This study was able to demonstrate that RAU is perhaps a more important disease in young adults than assumed earlier and that RAU prevalence is substantial as people grow older. Literature suggests that minor, major and herpetiform RAU have different peak ages of onset. Because NHANES III did not record diagnoses to that detailed extent of differentiation, we cannot comment on the issue. However, a large proportion had single ulcers, and the mean age of those with single ulcers was substantially lower than those with multiple ulcers. We cannot conclude much from this observation unless various physiological and biochemical factors purported to be associated with RAU, smoking habits and other such factors are evaluated in greater detail among different clinical presentations of RAU. The odds of RAU were almost double among men compared with women – this difference should be evaluated further because the difference in risk was unchanged upon our multivariable adjustment.

Although RAU occurs on both keratinized as well as non-keratinized mucosa (6), specific site predilections have never been clearly reported. Most RAU seen in this study occurred in the lower half of the oral cavity, mostly on non-keratinized mucosa, with the lower vestibule being the commonest site. Although slightly more proportion of RAUs occurred on the right side, the predominant area was the front of the oral cavity, mostly in the area of labial mucosa, the anterior part of the lower and upper vestibule, and commisures, which supports the general notion about the site of RAU occurrence. Neither occurrence of any oral mucosal co-morbidity nor any individual co-morbities were

associated with RAU. However, systemic co-morbidities and alteration in physiological state such as hormonal imbalances could be associated with RAU and is being investigated further.

Rivera-Hidalgo et al. (11) reported greater odds of RAU among those with a history of recurrent herpes labialis (RHL). We consider that clinical diagnosis of RHL may confound RAU diagnosis, unless vesicles are unambiguously demonstrated. Therefore, we chose a more objective measure of HSV exposure that is available in the NHANES III database, i.e. serum HSV-1 and HSV-2 antibody titer. The mean titers for both these virus did not differ between those with RAU and those without. When evaluated in multivariate models, the results remained same. We therefore conclude that HSV-1 and HSV-2 are not associated with RAU. Potential diagnostic misclassification is one explanation for the observation of RHL–RAU association by Rivera-Hidalgo et al. (11).

Racial/ethnic differences in the prevalence of RAU and those between age groups, sex, and census tract region were noted in this study. Initial impressions about varying prevalence by census tract regions, especially greater prevalence of RAU in the West may have suggested a role for some possible environment agent. However, geographical variation in distribution of people by their race/ethnic characteristic could be viewed as confounders. Lack of the geographical region effect as well as race/ethnicity effect in multivariable models supports the idea that the ethnic variability of RAU prevalence may have other basis. The significantly lesser crude odds of RAU in non-Hispanic Blacks and greater odds in 'Other' ethnic groups should be investigated further as there might be some possible genetic basis for these differences. Alternatively, cultural practices in oral habits, or food consumption could also account for these differences.

The two most significant observations were the confirmation that men are at greater risk for RAU; and compared with cigarette smokers, non-smokers have a greater risk of RAU; the issue of possible dose-dependent reduction of risk of RAU with smoking should be evaluated in future studies. We believe that further investigation into effects of cigarette smoking in the local oral milieu may shed light on the etiopathogenic mechanism of RAU, which remains an enigma even at now. The observation that mean serum insulin level is lower among RAU patients is being reported for the first time. Low serum insulin remained a significant factor in the multivariate models. Although causality cannot be inferred based on a one-time observation from a cross-sectional study, this observation can be explained in biomechanism terms.

Diabetes mellitus has been shown to have a deleterious influence on the healing of acute gastric lesions in an insulin-sensitive manner (40). These authors suggested that insulin could upregulate an insulin-like growth factor that could exert its healing effect on gastric mucosa. Another study (41) suggested that oral insulin supplementation exerts trophic effects, as well as systemic effects in the postweaning periods in rats. Furthermore, insulin and insulin-like growth factors have been implicated in gastrointestinal (gastric ulcers, colitis) regeneration following injury (42). Although the lower confidence level in our multivariable adjusted estimate is close to unity, the OR of 2.0 suggests a possible association that should be examined further. It is conceivable that insulin may also play a role, although a weak one, in maintaining oral mucosal integrity, and in helps in mucosal healing from RAU. If this were true, then impaired healing from RAU could be observed when insulin levels are low. Alternatively, if insulin plays a role in maintaining oral mucosal integrity, then low insulin levels may prime the mucosa for easy ulceration. Direct role for insulin may occur in relation to secretion of insulin in saliva, which may allow a direct interaction of insulin with oral mucosa. We believe that further investigations to examine mechanism-based hypotheses are warranted. Further studies will be needed to clarify the possible etiologic and predictive factors for RAU.

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