Associations of Serum Adiponectin and Leptin With Barrett's Esophagus

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Q9 **BACKGROUND & AIMS:** **Central adiposity is a risk factor for Barrett's esophagus (BE). Serum levels of adiponectin and leptin are deregulated in obese states and are implicated as putative mediators in the pathophysiology of esophageal columnar metaplasia. We describe associations between serum adiponectin and leptin levels with BE.**

METHODS: **Patients were recruited prospectively for a case–control study. Fasting serum levels of adiponectin and leptin were measured in 135 patients with BE and compared with 2 separate control groups: 133 subjects with gastroesophageal reflux disease (GERD) and 1157 colon screening controls.**

RESULTS: **Multivariate analyses adjusted for age, race, and waist-to-hip ratio showed that patients within the highest tertile of serum adiponectin level had decreased odds of BE compared with screening colonoscopy controls (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.22–0.80).** Q10 **This effect was more pronounced in males (OR, 0.35; 95% CI, 0.17–0.74) compared with females (OR, 0.71; 95% CI, 0.17–3.03). In comparisons of BE cases with GERD controls, subjects within the highest tertile of serum adiponectin level showed decreased odds of BE (OR, 0.65; 95% CI, 0.31–1.36), however, this was not statistically significant. Patients in the highest tertile of serum leptin level did not have a significantly increased risk of BE in comparison with GERD (OR, 1.32; 95% CI, 0.61–2.88) or screening colonoscopy controls (OR, 1.57; 95% CI, 0.82–3.04) in analyses including both sexes. Based on sex-specific analyses, sex did not significantly alter the association of leptin with odds of BE.**

CONCLUSIONS: **Serum adiponectin was associated inversely with BE and this effect was more pronounced in males, whereas serum leptin showed no evidence of association with BE in comparisons with multiple control groups. The exact mechanism, if any, by which these adipokines promote metaplasia in the esophagus needs to be explored further.**

Keywords: Adipokine; Esophagus; Epidemiology.

Q11 Q12 Q13 Obesity is a strong risk factor for Barrett's esophagus (BE) and esophageal adenocarcinoma.[1–4] Being obese increases the odds of esophageal cancer by approximately 1.5-fold in both sexes.[5] Obesity now is well recognized as a state of low-grade inflammation, and adipocyte dysfunction with increased secretion of inflammatory cytokines and adipokines has been associated with esophageal cancer and other cancers.

Leptin is an important hormone produced by adipocytes and its circulating levels are proportional to the total amount of fat mass.[6] A variety of factors affect serum leptin levels including short-term fasting, sleep deprivation, level of stress, degree of tissue inflammation, medications, and physical exercise.[7] Obese individuals have markedly increased levels of circulating leptin and they show leptin resistance. Leptin binds the leptin receptor at the cell surface and the signal is transduced intracellularly through the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) pathway.[8] Once STAT3 is activated by phosphorylation, it is able to translocate itself to the nucleus, where it can regulate gene expression.[9,10] At the molecular level, leptin is pro-angiogenic, proinflammatory, and mitogenic. Adiponectin is a protein encoded by the ADIPOQ gene and also secreted by the Q14

Abbreviations used in this paper: **BE, Barrett's esophagus; BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; ORa, adjusted odds ratio; STAT3, signal transducer and activator of transcription 3.**

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white adipose tissue. It circulates in 3 multimeric forms: low-molecular-weight, middle-molecular-weight, and high-molecular-weight adiponectin. The adiponectin protein contains 4 major domains and the structure of its globular region closely resembles that of tissue necrosis factor-α. Adiponectin transmits its signal through AdipoR1 and AdipoR2 receptors by threonine-mediated activation of 5' adenosine monophosphate-activated protein kinase as well as peroxisome proliferator-activated receptor α–mediated signaling.[11,12] Adiponectin plays an important role in glucose flux and energy metabolism, up-regulation of uncoupling proteins, and protection from endothelial dysfunction.[13]

Studies on serum leptin and tissue leptin-receptor expression have shown positive associations with BE.[14,15] Levels of serum total adiponectin have shown either no evidence of association with BE,[14] or shown a protective effect for low-molecular-weight adiponectin.[16] Other studies have suggested that the effect of adipokines on esophageal metaplasia may be sex-specific.[17] We sought to clarify these relationships further in a case–control study comparing patients with BE with gastroesophageal reflux disease (GERD) controls and population controls. We hypothesized that serum leptin levels would be associated positively with increased risk of BE, whereas increasing serum adiponectin level would show an inverse association.

Methods

Study Population

Patients were recruited from University Hospitals Case Medical Center and Cleveland Clinic Foundation between January 2005 and May 2009. Potential participants were recruited at the time of their endoscopy visit that was scheduled for management of refractory reflux, BE surveillance, or colorectal cancer screening. The majority of BE cases were referred from outside providers. Criteria for recruitment of BE cases and both control groups have been described elsewhere.[18] Patients in the GERD control group were recruited from subjects with refractory GERD symptoms that were defined as a report of persistent reflux that was not relieved by an adequate dose of proton pump inhibitor warranting further endoscopic evaluation. The diagnosis of GERD was established based on the assessment of the patient's treating physician. pH probe testing was not used to establish a diagnosis of pathologic reflux. Patients in the screening colonoscopy group did not undergo routine upper endoscopy. Patients could not be included in the screening colonoscopy group if they had polyps on a prior endoscopic examinations, history of inflammatory bowel disease, or colorectal cancer. In brief, we enrolled 135 patients with BE, 133 patients with GERD but no endoscopic or histologic evidence of BE, and 1157 screening colonoscopy controls. This sample size was calculated based on the assumption that at least 30% of cases would have increased serum adipokine levels, body mass index (BMI), waist-to-hip ratio, and other risk factors relevant to the pathophysiology of BE and our goal to identify risk factors that increased the odds of BE by 2- to 4-fold. This study was approved by the Institutional Review Board of the Case Comprehensive Cancer Center and written informed consent was obtained from all participants.

Serum Adiponectin and Leptin

Fasting blood samples were taken from each subject before the endoscopic procedure and placed on ice for processing. Grossly lipemic and icteric specimens were excluded. Samples were centrifuged under refrigeration and separated serum was aliquoted into cryovials and stored at -70°C. Serum leptin and total adiponectin concentrations were measured by an enzyme-linked immunosorbent assay (Linco, St Charles, MO) according to the manufacturer's instructions. All measurements of serum adipokine levels were performed at the Dahms Clinical Research Unit Laboratory of the Case Western Reserve University.

Statistical Methods

Simple descriptive statistics were performed to describe the risk factor frequencies among cases and controls. Univariate logistic regressions were completed to calculate odds ratios (ORs) and the associated 95% confidence intervals (CIs) on all variables of interest. Multivariate regression analyses were conducted to adjust for baseline differences among study groups. OR estimates were adjusted for age, sex (male vs female), race (white vs non-white), and central adiposity (waist-to-hip ratio). For variables that were split into tertiles, ORs and the associated 95% CIs were calculated by comparing the highest tertiles with the lowest. Cut-off points for tertile analysis of adiponectin and leptin first were determined separately for each sex for the entire study group. These sex-specific tertiles then also were used in the subsequent analysis of BE cases with screening colonoscopy as well as GERD controls. Multivariate sex-specific regression models were adjusted for age, race, and waist-to-hip ratio. The Cochran Armitage test was applied in the analysis of trends. All tests of statistical significance were 2-sided and P values less than .05 were considered significant. Statistical analyses were performed using the Statistical Analysis Systems software package 9.3 (Cary, NC).

Results

Baseline Characteristics

Cases with BE were older than subjects in both control groups. There were no significant differences in BMI between cases and both control groups. The waist-to-hip