HHS Public Access

Author manuscript

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Clin Gastroenterol Hepatol. 2015 December ; 13(13): 2256–2264.e3. doi:10.1016/j.cgh.2015.01.009.

Adiponectin may modify the risk of Barrett's esophagus in patients with gastroesophageal reflux disease

Lucy M Almers, MPH[1], **James E Graham, PhD**[2], **Peter J Havel, PhD**[2], and **Douglas A Corley, MD, PhD**[1]

[1]Division of Research, Kaiser Permanente, Oakland [2]Department of Molecular Biosciences, School of Veterinary Medicine and Department of Nutrition, University of California, Davis

Abstract

Background & Aims—Abdominal obesity and increasing body mass index are risk factors for esophageal adenocarcinoma and its main precursor, Barrett's esophagus; however, there are no known biological mechanisms for these associations or regarding why only some patients with gastroesophageal reflux disease develop Barrett's esophagus. We evaluated the association between Barrett's esophagus and multimers of an adipose-associated hormone, adiponectin.

Methods—We conducted a case-control study evaluating the associations between adiponectin (total, high molecular weight, and low/medium molecular weight) and Barrett's esophagus within the Kaiser Permanente Northern California population. Patients with a new diagnosis of Barrett's esophagus (cases) were matched to patients with gastroesophageal reflux disease (GERD) without Barrett's esophagus and to population controls.

Results—Complete serologic and epidemiologic data were available for 284 cases, 294 GERD controls, and 285 population controls. Increasing adiponectin levels were a risk factor for Barrett's esophagus among patients with gastroesophageal reflux disease (total adiponectin fourth vs. first quartile odds ratio [OR]=1.96; 95% confidence interval (CI) 1.17–3.27; high molecular weight adiponectin OR=1.65; 95% CI 1.00–2.73; low/medium molecular weight adiponectin OR=2.18; 95% CI 1.33–3.56, but not compared with population controls. The associations were significantly

Corresponding author: Douglas Corley, MD, PhD, MPH, Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612, Douglas.Corley@kp.org.

Disclosures

None

Author Contributions

Lucy M Almers statistical analysis; analysis and interpretation of data; drafting of manuscript

James E Graham assisted in conducting the study; provided technical support; critical revision of the manuscript for important intellectual content;

Peter J Havel assisted in conducting the study; provided technical support; critical revision of the manuscript for important intellectual content;

Douglas A Corley study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; collected data; and assisted in interpreting data and reviewed manuscript; obtained funding

stronger among patients reporting frequent GERD symptoms and among smokers (p-values interaction <0.01).

Conclusion—Adiponectin levels are positively associated with the risk of Barrett's esophagus among patients with GERD and among smokers, but not among population controls without GERD symptoms. Higher adiponectin concentrations may either independently contribute to the aberrant healing of esophageal injury into Barrett's esophagus or be a marker for other factors.

Keywords

esophageal adenocarcinoma; adiponectin; BMI; Barrett's esophagus; adipokines

Introduction

The incidence of esophageal adenocarcinoma has increased over 500% in the United States over the last three decades; it accounts for >2% of male cancer deaths.(1, 2) Barrett's esophagus likely represents a metaplastic healing response to esophageal injury, typically from gastroesophageal reflux disease (GERD);(3) its presence increases the risk for esophageal adenocarcinoma by 30–40 fold.(4) Barrett's esophagus is associated with obesity, especially abdominal obesity, (5, 6) although the biological links between obesity, Barrett's esophagus, and cancer are unclear. (5, 7, 8)

Circulating adiponectin, an adiposity-associated hormone, is inversely associated with adiposity and insulin resistance;(9, 10) it may represent a mechanistic link between Barrett's esophagus and obesity.(11–13) Animal models suggest that adiponectin influences the healing response of the gastrointestinal mucosa.(14) Mice lacking adiponectin, for example, had more ethanol-induced gastric injury than normal mice, while adiponectin administration improved gastric mucosal repair.(14) Adiponectin is also a potentially modifiable factor, given adiponectin agonists and homologs are currently being studied as potential therapeutic agents. (15, 16)

We evaluated the associations between circulating adiponectin subtypes and the risk of Barrett's esophagus using two control groups: patients diagnosed with GERD and population controls.

Methods

Study Design and Population

We conducted a nested case-control study within Kaiser Permanente Northern California (KPNC).(17) Patients were 18–79 years of age and continuously members for ≥2 years before their index date. The design and analyses were approved by the KPNC institutional review board (September, 2002).

Case Definition

Cases were eligible KPNC members with a new diagnosis of Barrett's esophagus between October 2002 and September 2005, identified using the International Classification of Disease, Ninth Revision (ICD-9) code 530.2, defined at KPNC as "Barrett's esophagitis." A

gastroenterologist (DAC) reviewed endoscopy and pathology records. Patients were included if there was a visible length of columnar-type epithelium proximal to the gastro-esophageal junction/gastric folds, and an esophageal biopsy showed specialized intestinal epithelium (18) (after pathologist slide review (GJR)). Patients were excluded if they had only gastric-type or columnar metaplasia without intestinal metaplasia; lacked an esophageal biopsy or had biopsies only of a mildly irregular squamocolumnar junction; had a prior diagnosis of Barrett's esophagus; or had esophageal cancer (dysplasia was included). The index date was the date of Barrett's esophagus diagnosis.

GERD Controls

GERD control members had all of the following before entry: a GERD-related ICD-9 code (530.11 [reflux esophagitis] or 530.81 [gastro-esophageal reflux]); a prescription for ≥90 days' use of a histamine-2 receptor antagonist or a proton pump inhibitor in the previous year; no prior diagnosis of Barrett's esophagus; and a recent esophagogastroduodenoscopy that did not show esophageal columnar metaplasia of any type.

Population Controls

Population controls were randomly selected from the at-risk (no prior Barrett's esophagus diagnosis) KPNC membership, using risk set sampling.(19) The index date for controls was the midpoint of each 2–3 month case selection interval. The population and GERD controls were frequency matched to cases by sex, age at index date (5-year age groups), and geographic region (medical facility).

Exposure Measurements

Serum samples were stored at −80°C; adiponectin is stable frozen.(20, 21) Concentrations were assayed in duplicate, using mixed cases and controls, in an experienced adiponectin laboratory (PJH). High molecular weight adiponectin measurements used enzyme-linked immunosorbent assay (ALPCO); total measurements used radioimmunoassay (Millipore). We compared same-sample inter-assay values and adjusted for differences with a conversion factor. The "adiponectin ratio" equals high molecular weight adiponectin/total adiponectin.

All subjects completed: an in-person interview of GERD symptoms and use of medications, tobacco, and alcohol (all for year prior to index date and longer exposures); a validated food frequency questionnaire (Block 1998 full-length);(22) and measurements of height, weight, waist (obtained standing at the iliac crest)/thigh circumferences and serum Helicobacter pylori serum antibody status. Examinations used trained interviewers, most commonly at the subject's home. GERD assessments used a validated symptom questionnaire (23) for heartburn or acid regurgitation.

Statistical Analysis

The study employed standard techniques for unpaired case-control studies, including unconditional logistic regression.(19, 24) Comparisons of proportions used the binomial distribution (Stata version 10.1; Stata Corp, College Station, TX). Continuous adiponectin measures used log-transformed values. Quartiles used distributions among the population controls and gender-specific quartiles for gender stratified analyses.

We evaluated as potential confounders: education (<7, 7–9, 10–11, 12+ years); smoking status (≥20 vs. < 20 lifetime-packs);(25) alcohol (ever vs. never drank alcohol); total daily calories, antioxidants (vitamin A, C and E, carotene and selenium), fat intake, fruits, vegetables, and iron; multivitamins; GERD symptom frequency (<weekly vs. ≥weekly); a comorbidity index;(26, 27) helicobacter pylori serum antibody status; aspirin and nonsteroidal anti-inflammatory medication use; body mass index (BMI), waist circumference, and race. We evaluated for effect modification by race, gender, smoking and GERD symptom frequency using cross-product terms in the crude logistic regression model and stratum-specific odds ratios (ORs).(28)

A potentially confounding variable was retained if it changed the main effect OR by ≥10% for at least two adiponectin variables (total, high molecular weight adiponectin, low/medium molecular weight, and ratio). Final models were therefore adjusted for waist circumference, race, and the main frequency-matched variables (sex and age). The covariates were evaluated separately for both population-based controls and GERD controls; the variables which changed the OR by >10% were similar for both comparison groups, thus the same confounding structure was utilized in the model for both comparisons

Results

Patient Characteristics

Complete data were available for 96.8% (n=923) of all interviewed subjects (Table 1); thirty persons were excluded due to missing values for: waist (n=4), serum availability for adiponectin measurement (n=25), and race/ethnicity (n=1). GERD controls had a lower mean weight (184.7 lbs.) than cases (191.5 lbs.) or population controls (191.8 lbs.). Cases were more likely to have at least weekly GERD symptoms (80.0%) (vs. GERD controls [73.4%] or population controls [28.2%]) and to be non-Hispanic whites (87.4%) (vs. population controls [84.9%] or GERD controls [80.5%]).

Cases vs. GERD Controls

Participants in the fourth (vs. first) quartile of total and low+medium weight adiponectin were twice as likely to have Barrett's esophagus (total adiponectin OR=1.96; 95% CI 1.17–3.27; low+medium weight OR= 2.18; 95% CI 1.33, 3.56) (Table 2, Figure 1). Similarly, participants in the fourth quartile of high molecular weight adiponectin were more likely to have Barrett's esophagus (OR=1.65; 95% CI 1.00–2.73) (Table 2, Figure 1). Similar significant associations were seen for continuous measures of total, high molecular weight, and low/medium molecular weight adiponectin (Table 2).

Cases vs. Population Controls

Increasing adiponectin levels were associated with Barrett's esophagus among population controls with GERD symptoms, but not among population controls overall or population controls with minimal or no GERD symptoms (p-value interaction total adiponectin, P<0.001) (Tables 2&3, Figure 2). Continuous measures of total and high molecular weight adiponectin were positively associated with Barrett's esophagus among cases/population controls with frequent GERD symptoms (≥weekly), comparable to subjects in the larger

physician-defined GERD control group (OR 1.68, total adiponectin; 95% CI 1.01–2.80; OR 1.50, high molecular weight adiponectin; 95% CI 1.04–2.15) (Table 3). Analyses by quartile had overall similar directions, although with wider confidence intervals.

Smoking

Total adiponectin—For comparisons with GERD controls, there were positive associations between total, high molecular weight, and low/medium molecular weight adiponectin and Barrett's esophagus among "ever smokers" (OR=1.83, total adiponectin; 95% CI 1.20–2.78; OR=1.46, high molecular weight adiponectin; 95% CI 1.09–1.97; OR=2.11, low/medium molecular weight adiponectin; 95% CI 1.27–3.49) but not among "never smokers" (Supplementary Table 1, Figure 3). The associations were strongest among current smokers, although with limited power to evaluate current smokers (Supplementary Table 1, Figure 3). Similar positive associations between total, high molecular weight, and medium weight adiponectin and Barrett's esophagus were also seen in the case vs. population control comparison group for ever smokers, but not never smokers (not shown).

Stratifications by sex

The associations between total adiponectin levels and Barrett's esophagus were somewhat stronger among women than among men, among GERD controls (continuous measure, women: OR=2.27; 95% CI 1.15–4.47; men: OR=1.50; 95% CI 1.02–2.22; p-value interaction=0.10) (Supplementary Table 2). Low/medium molecular weight adiponectin had significant associations or strong trends with the risk of Barrett's esophagus among both men and women, whereas high molecular weight adiponectin showed significant associations only among women (Supplementary Table 2). For cases vs. population controls, females showed significant associations for total adiponectin, high molecular weight adiponectin and adiponectin ratio, but not for low/medium molecular weight adiponectin (data not shown).

Stratifications by BMI

The nonsignificant trends for associations between adiponectin and Barrett's esophagus were stronger among persons with a normal BMI (e.g. log-transformed total adiponectin, continuous value OR=2.22, 95% CI 0.98, 5.04), than among overweight (OR=1.32, 95% CI 0.76, 2.30) or obese persons (OR=1.15, 95% CI 0.68, 1.94). Similar patterns were seen for high and low+medium weight adiponectin multimers (Supplementary Table 3).

Influence of proton pump inhibitors

Among the population controls, mean adiponectin levels were similar between PPI users vs. non-users (mean 11.88 vs. 12.99, respectively; p=0.24). A logistic regression model adjusted for sex, age, and BMI demonstrated no significant association between adiponectin levels and PPI use (data not shown).

Evaluation of Assumptions

We evaluated previously reported associations for adiponectin, using the population controls.(29–32) As expected, mean adiponectin levels decreased with rising BMI (p<

0.0001); were lower among men (p<0.001); and increased with age (p<0.0001). Unlike some prior reports, it was not correlated with smoking status (ever vs. never).(32)

If adiponectin mediates the association between waist circumference and Barrett's esophagus, we would expect the association between adiponectin and Barrett's esophagus to diminish after controlling for obesity. On the contrary, for cases vs. GERD controls, the association for low/medium molecular weight adiponectin actually strengthened after adjusting for BMI (unadjusted: OR=1.45; 95% CI 1.01–2.08; adjusted: OR=1.55; 95% CI 1.07–2.25) and for both BMI and waist circumference (OR=1.80; 95% CI 1.22–2.65).

Discussion

These results suggest that increasing serum concentrations of total adiponectin, high molecular weight adiponectin and low/medium molecular weight adiponectin are associated with an increased risk of Barrett's esophagus among people with a physician-assigned GERD diagnosis, population controls with frequent self-reported GERD symptoms and smokers, but not among persons without GERD symptoms and nonsmokers.

The current study adds knowledge regarding the associations between adiponectin and the body's response to injury. Barrett's esophagus is thought to result from an aberrant healing response to esophageal injury, most commonly gastroesophageal reflux. A positive association between adiponectin and esophageal healing is biologically plausible; animal models demonstrate it is strongly associated with gastrointestinal mucosal healing after caustic injury.(14) Adiponectin may modify pathways for cell injury and repair, such as the nitric oxide and interleukin pathways.(11, 12) Smoking is also associated with both the risk of esophagitis and the risk of Barrett's esophagus independent of GERD.(33) Two potential explanations for our findings include: 1) higher adiponectin levels may increase the risk of a metaplastic healing response (i.e. Barrett's esophagus) in response to GERD-induced injury and smoking; or 2) higher adiponectin levels may increase the risk of esophagitis, which is associated with both smoking and GERD. The second explanation is less likely given that adiponectin was not independently associated with either smoking or GERD symptoms among our population controls (data not shown).

Adiponectin's associations with mucosal healing may differ from its other roles with carcinogenesis. Adiponectin levels have been inversely associated with the risk of prostate, colon, gastric, endometrial and breast cancers.(34–38) Adiponectin inhibits leptin-induced cell growth (39), suggesting that high serum concentrations may protect against cancer. A study by Yildirim et al. found lower levels of adiponectin among patients with esophageal cancer (n=75 cases, 13 with adenocarcinoma).(40) Studies in cancer patients, however, have difficulty excluding changes in adiponectin caused by the cancer, such as alteration of diet, exercise or metabolism. Another study, which looked at the relationship between adiponectin receptor expression in esophageal adenocarcinoma cancer cells,(41) found that greater amounts of visceral fat were associated with greater expression of the adiponectin receptor-2, independent of serum adiponectin levels.(41)

The current results differ from two of three prior smaller studies of Barrett's esophagus. One found lower levels of low molecular weight serum adiponectin among 112 Barrett's esophagus patients vs. GERD-control patients (third vs. first tertiles: OR=0.33; 95% CI 0.16–0.69) and no significant associations for total or high molecular weight adiponectin; the study did not include population controls.(42) The second study found lower total adiponectin levels among 177 Barrett's esophagus cases vs. population controls (third vs. first tertiles: OR= 0.56; 95% CI: 0.32–0.98).(43) In contrast, the third study found a non-significant trend for a positive association between adiponectin and Barrett's esophagus,(44) and significant positive associations among white males (fourth vs. first quartiles OR= 3.27; 95% CI 1.06–10.05). (44) We cannot fully account for the differences between the prior studies and the current findings, although some groups of patients without GERD in our study did have inverse associations (Table 3) and some of the other studies adjusted for smoking, GERD, and hiatal hernia whereas we evaluated these primarily as sources of interaction. All three prior studies had much smaller sample sizes (decreasing the power to look for interaction), slightly younger populations, and some had fewer smokers in the control groups.(41–44) Similar to the current study, Thompson included only new diagnoses of Barrett's esophagus, whereas Rubenstein included both prevalent and new diagnoses and reported somewhat lower mean adiponectin levels. (42–44)

The current results run counter to the general inverse associations between adiponectin levels and obesity, and the positive associations between abdominal obesity and Barrett's esophagus.(5, 45, 46) However, prior positive associations between abdominal obesity and Barrett's esophagus were mainly observed in comparisons with population based controls; no strong associations were found among patients with GERD.(5) Thus, given the known associations between adiponectin and mucosal healing, our current results represent a potential mechanism whereby only some patients with GERD develop Barrett's esophagus. The associations between abdominal obesity and Barrett's esophagus among population controls may not be strongly mediated by adiponectin.

There are several strengths of the current study. First, positive associations between adiponectin and Barrett's esophagus were found in both population controls with self-reported GERD symptoms and patients with physician-assigned GERD diagnoses. Second, our analyses showed the expected associations between adiponectin levels and sex, age, and BMI; this also makes bias in the laboratory or with patient sampling less likely. Third, we studied a large group of patients with a new diagnosis of Barrett's esophagus within a community-based population, thereby minimizing selection bias found persons with prevalent Barrett's esophagus. Fourth, the number of cases is almost twice as large as the largest previously published study (43), providing greater power to evaluate interactions. Fifth, the two control groups allowed a separate evaluation of why only some GERD patients develop Barrett's esophagus. Sixth, the data were of high quality, with validated questionnaires, detailed anthropometric measurements, direct review of the endoscopy reports and manual pathology slide review.

The analyses have several potential limitations. First, case-control studies cannot establish cause and effect; adiponectin levels may differ without it causing Barrett's esophagus.(19) We cannot exclude incomplete control of confounding. Second, we did not measure the

adiponectin levels at exactly the time the Barrett's esophagus developed, given that time is unknown. Fourth, low and medium molecular weight adiponectin were calculated through subtraction of measured high molecular weight adiponectin. While the low and medium molecular weight forms of adiponectin together are the predominant forms in the circulation (47) high molecular weight adiponectin appears to be the most bioactive form in terms of regulating glucose homeostasis and insulin sensitivity.(10) The finding of a borderline stronger association between adiponectin and Barrett's esophagus among women vs. men is interesting, given women are at lower risk than men for this condition. Although adiponectin levels are known to differ between men and women, the interaction term was of marginal statistical significance (p=0.10) and there may be sex-specific differences in its biological activities.

In summary, in a community-based population, there was an association between increasing levels of serum adiponectin multimers and a new diagnosis of Barrett's esophagus, among patients with GERD. This association was stronger among smokers, and among persons with more frequent GERD. These results suggest a potential for a direct mechanistic role for adiponectin in the process of mucosal healing that may cause Barrett's esophagus, although is also possible that circulating adiponectin concentrations are a marker for another process, such systemic inflammation related to Barrett's esophagus. Although the results run counter to the expected direction of obesity's general associations with Barrett's esophagus (and with adiponectin levels), they represent one of the first potential biological risk factors identified for why only some patients with GERD and smoking develop Barrett's esophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: This work was supported by National Institute of Diabetes and Digestive and Kidney Disease grants R56 DK087748 and RO1 DK63616

Abbreviations

BMI	body mass index
CI	confidence interval
GERD	gastroesophageal reflux disease
ICD-9	International Classification of Disease
KPNC	Kaiser Permanente Northern California
OR	odds ratio

References

1. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol. 1999; 26:2–8. [PubMed: 10566604]

2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005; 97:142–6. [PubMed: 15657344]
3. Reynolds RP. Pathophysiology and investigation of Barrett's esophagus. Can J Gastroenterol. 1997; 11 (Suppl B):41B–44B. [PubMed: 9113798]
4. Sikkema M, de Jonge PJ, Steyerberg EW, et al. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2010; 8:235–44. quiz e32. [PubMed: 19850156]
5. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology. 2007; 133:34–41. quiz 311. [PubMed: 17631128]
6. Murray L, Romero Y. Role of obesity in Barrett's esophagus and cancer. Surg Oncol Clin N Am. 2009; 18:439–52. [PubMed: 19500735]
7. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control. 2004; 15:35–43. [PubMed: 14970733]
8. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2006; 4:566–72. [PubMed: 16630761]
9. Havel PJ. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes. 2004; 53 (Suppl 1):S143–51. [PubMed: 14749280]
10. Swarbrick MM, Havel PJ. Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. Metabolic syndrome and related disorders. 2008; 6:87–102. [PubMed: 18510434]
11. Ajuwon KM, Spurlock ME. Adiponectin inhibits LPS-induced NF-kappaB activation and IL-6 production and increases PPARgamma2 expression in adipocytes. Am J Physiol Regul Integr Comp Physiol. 2005; 288:R1220–5. [PubMed: 15604306]
12. Chen H, Montagnani M, Funahashi T, et al. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem. 2003; 278:45021–6. [PubMed: 12944390]
13. Corley DA. Obesity and the rising incidence of oesophageal and gastric adenocarcinoma: what is the link? Gut. 2007; 56:1493–4. [PubMed: 17938426]
14. Yamamoto S, Watabe K, Araki H, et al. Protective role of adiponectin against ethanol-induced gastric injury in mice. Am J Physiol Gastrointest Liver Physiol. 2012
15. Kupchak BR, Garitaonandia I, Villa NY, et al. Antagonism of human adiponectin receptors and their membrane progesterone receptor paralogs by TNFalpha and a ceramidase inhibitor. Biochemistry. 2009; 48:5504–6. [PubMed: 19453184]
16. Miele M, Costantini S, Colonna G. Structural and Functional Similarities between Osmotin from Nicotiana Tabacum Seeds and Human Adiponectin. PLoS ONE. 2011; 6:e16690. [PubMed: 21311758]
17. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992; 82:703–10. [PubMed: 1566949]
18. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. Gastroenterology. 2004; 127:310–30. [PubMed: 15236196]
19. Rothman, KJGS. Modern Epidemiology. Philadelphia, PA: Lippencott-Raven; 1998.
20. Choi KM, Lee J, Lee KW, et al. Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. Clinical endocrinology. 2004; 61:75–80. [PubMed: 15212647]
21. Pischon T, Hotamisligil GS, Rimm EB. Adiponectin: stability in plasma over 36 hours and within-person variation over 1 year. Clinical chemistry. 2003; 49:650–2. [PubMed: 12651819]
22. Block G, Thompson FE, Hartman AM, et al. Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period. J Am Diet Assoc. 1992; 92:686–93. [PubMed: 1607564]
23. Locke GR, Talley NJ, Weaver AL, et al. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc. 1994; 69:539–47. [PubMed: 8189759]

24. Breslow, NEDN. Statistical methods in cancer research. Volume 1: the analysis of case-control studies. Lyon, France: International Agency for Research on Cancer; 1980.
25. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. 1978; 118:1–120. [PubMed: 742764]
26. Zhao Y, Ash AS, Ellis RP, et al. Predicting pharmacy costs and other medical costs using diagnoses and drug claims. Med Care. 2005; 43:34–43. [PubMed: 15626932]
27. Zhao Y, Ellis RP, Ash AS, et al. Measuring population health risks using inpatient diagnoses and outpatient pharmacy data. Health Serv Res. 2001; 36:180–93. [PubMed: 16148968]
28. Hosmer, DWLS. Applied logistic regression. New York, NY: Wiley; 2000.
29. Isobe T, Saitoh S, Takagi S, et al. Influence of gender, age and renal function on plasma adiponectin level: the Tanno and Sobetsu study. Eur J Endocrinol. 2005; 153:91–8. [PubMed: 15994750]
30. Kern PA, Di Gregorio GB, Lu T, et al. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes. 2003; 52:1779–85. [PubMed: 12829646]
31. Nishizawa H, Shimomura I, Kishida K, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes. 2002; 51:2734–41. [PubMed: 12196466]
32. Takefuji S, Yatsuya H, Tamakoshi K, et al. Smoking status and adiponectin in healthy Japanese men and women. Prev Med. 2007; 45:471–5. [PubMed: 17689602]
33. Cook MB, Shaheen NJ, Anderson LA, et al. Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012; 142:744–53. [PubMed: 22245667]
34. Goktas S, Yilmaz MI, Caglar K, et al. Prostate cancer and adiponectin. Urology. 2005; 65:1168–72. [PubMed: 15922427]
35. Ishikawa M, Kitayama J, Kazama S, et al. Plasma adiponectin and gastric cancer. Clin Cancer Res. 2005; 11:466–72. [PubMed: 15701829]
36. Mantzoros C, Petridou E, Dessypris N, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab. 2004; 89:1102–7. [PubMed: 15001594]
37. Petridou E, Mantzoros C, Dessypris N, et al. Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. J Clin Endocrinol Metab. 2003; 88:993–7. [PubMed: 12629074]
38. Wei EK, Giovannucci E, Fuchs CS, et al. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst. 2005; 97:1688–94. [PubMed: 16288122]
39. Ogunwobi OO, Beales IL. Globular adiponectin, acting via adiponectin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. Mol Cell Endocrinol. 2008; 285:43–50. [PubMed: 18313838]
40. Yildirim A, Bilici M, Cayir K, et al. Serum adiponectin levels in patients with esophageal cancer. Jpn J Clin Oncol. 2009; 39:92–6. [PubMed: 19116211]
41. Howard JM, Beddy P, Ennis D, et al. Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. Br J Surg. 2010; 97:1020–7. [PubMed: 20632267]
42. Rubenstein JH, Kao JY, Madanick RD, et al. Association of adiponectin multimers with Barrett's oesophagus. Gut. 2009; 58:1583–9. [PubMed: 19570765]
43. Thompson OM, Beresford SA, Kirk EA, et al. Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. Obesity (Silver Spring). 2010; 18:2204–11. [PubMed: 20111023]
44. Garcia JM, Splenser AE, Kramer J, et al. Circulating inflammatory cytokines and adipokines are associated with increased risk of Barrett's esophagus: a case-control study. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2014; 12:229–238. e3. [PubMed: 23954649]
45. Kramer JR, Fischbach LA, Richardson P, et al. Waist-to-hip ratio, but not body mass index, is associated with an increased risk of Barrett's esophagus in white men. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2013; 11:373–381. e1. [PubMed: 23220167]

46. Kubo A, Cook MB, Shaheen NJ, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium. Gut. 2013; 62:1684–91. [PubMed: 23355549]

47. Pajvani UB, Hawkins M, Combs TP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem. 2004; 279:12152–62. [PubMed: 14699128]

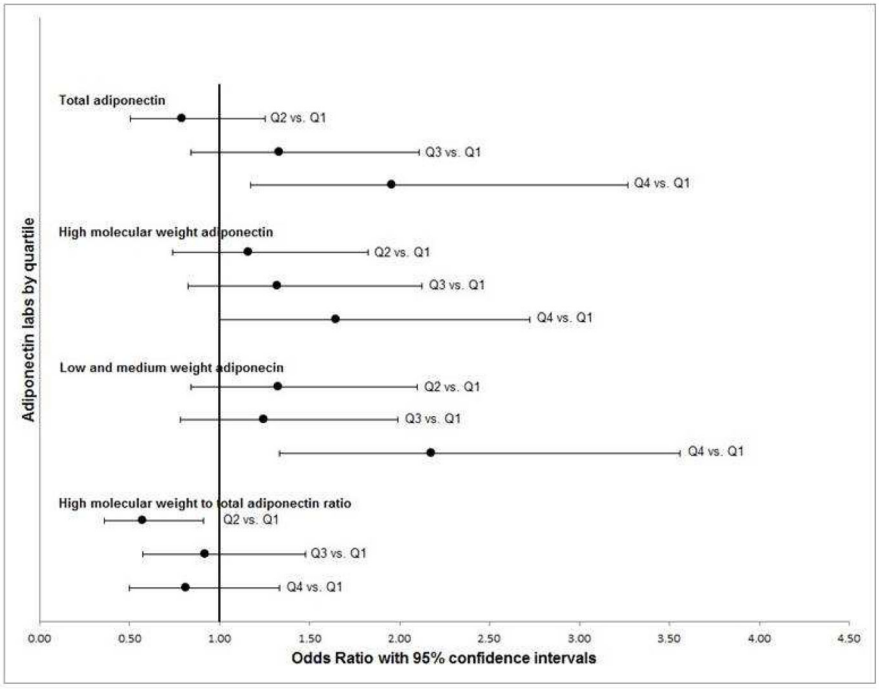

Fig. 1. Adiponectin and Barrett's esophagus: case vs. GERD controls

Odds ratios (black dots) and 95% confidence intervals (black bars) for adiponectin quartiles adjusted for sex, age, race/ethnicity and waist circumference.

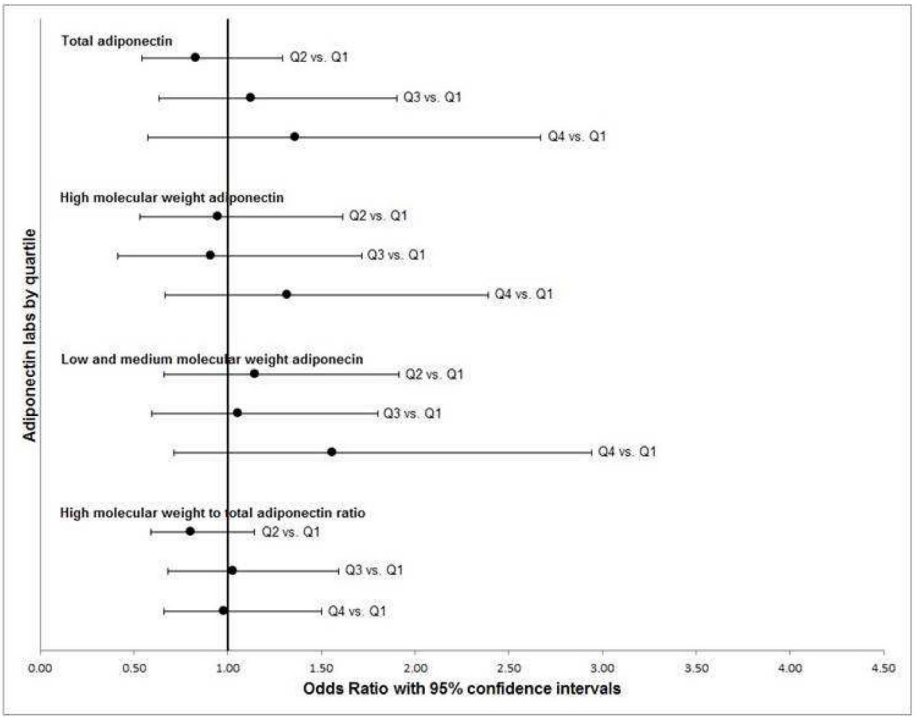

Fig. 2. Adiponectin and Barrett's esophagus: case vs. population controls

Odds ratios (black dots) and 95% confidence intervals (black bars) for adiponectin quartiles adjusted for sex, age, race/ethnicity and waist circumference.

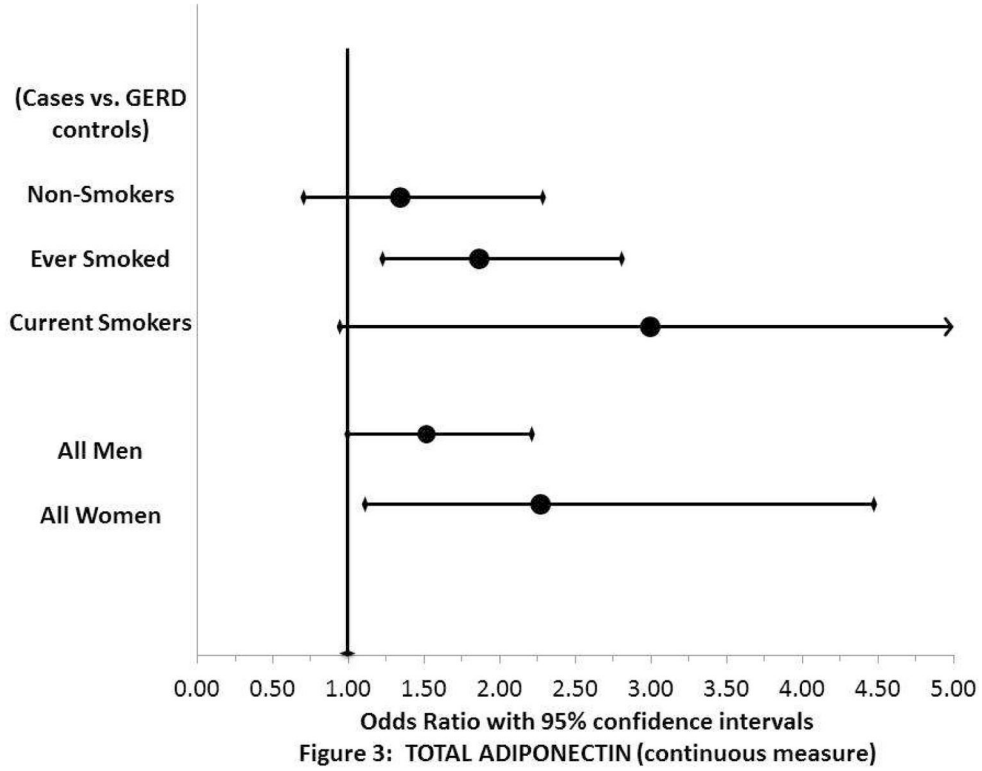

Fig. 3. Adiponectin and Barrett's esophagus: cases vs. GERD control, stratified by smoking status and sex

Stratified odds ratios (black dots) and 95% confidence intervals (black bars) for adiponectin log transformed concentrations adjusted for age, race/ethnicity and waist circumference.

Table 1

Characteristics of Study Groups

	Cases	Population Controls	GERD[2] Controls
No. of subjects, n (%)	310 (100.0%)	305 (100.0%)	308 (100.0%)
Age mean (SD[1])	62 (±10.7)	62 (±10.2)	62 (±10.7)
Age, n (%)			
20–39	7 (2.3%)	9 (3.0%)	11 (3.6%)
40–59	118 (38.1%)	102 (33.4%)	111 (36.0%)
60–79	185 (59.7%)	194 (63.6%)	186 (60.4%)
Race, n (%)			
Non-Hispanic white	271 (87.4%)	259 (84.9%)	248 (80.5%)
Black	4 (1.3%)	16 (5.2%)	20 (6.5%)
Hispanic	24 (7.7%)	12 (3.9%)	20 (6.5%)
Asian	3 (1.0%)	8 (2.6%)	7 (2.3%)
Other	8 (2.6%)	10 (3.3%)	13 (4.2%)
Sex, n (%)			
male	227 (73.2%)	208 (68.2%)	212 (68.8%)
Smoking status (ever smoked), n (%)	206 (66.5%)	170 (55.7%)	183 (59.4%)
GERD score[3], n (%)			
Any GERD[2] symptoms	289 (93.2%)	185 (60.7%)	289 (93.8%)
At least weekly	248 (80.0%)	86 (28.2%)	226 (73.4%)
Current weight (kg), mean (SD)	86.9 (±21.4)	87.0 (±18.8)	83.8 (±16.8)
Waist (cm[5]), mean (SD[1])	100.7 (±14.9)	99.1 (±17.5)	97.2 (±14.3)
BMI[6], mean (SD[1])	29.4 (±6.1)	29.4 (±5.8)	28.8 (±5.2)
BMI[6], n (%)			
underweight	5 (1.6%)	2 (0.7%)	4 (1.3%)
normal	60 (19.4%)	68 (22.3%)	63 (20.5%)
overweight	122 (39.4%)	116 (38.0%)	134 (43.5%)
obese	123 (39.7%)	119 (39.0%)	107 (34.7%)
Adiponectin multimers, mean (SD[1])			
Total (μg/ml[7])	12.8 (±7.7)	12.1 (±6.7)	11.7 (±6.8)
High Molecular Weight (HMW) (μg/ml[7])	3.4 (±2.9)	3.2 (±2.6)	3.1 (±2.7)
Low + Medium Molecular Weight (μg/ml[7])	4.3 (±2.0)	4.1 (±1.8)	3.9 (±1.7)
Ratio: HMW/total	0.40 (±0.1)	0.40 (±0.1)	0.40 (±0.1)

[1] SD= standard deviation

[2] GERD = gastroesophageal reflux disease

[3] GERD score represents patient's report of frequency of GERD symptoms, which isn't a criterion for GERD diagnosis. Thus, "any GERD" will not be 100% among GERD control group subjects.

[4] lb = weight in pounds

[5] cm= height in centimeters

[6] BMI=body mass index categories based on international standards as presented by the ‘World Health Organization Global Database on Body Mass Index’

[7] μg/ml= molecular weight in micro grams per milliliter

Table 2

Adiponectin and Barrett's esophagus: cases vs. population and GERD[3] control groups

	Counts			Cases vs. Population Controls		Cases vs. GERD[3] Controls	
	Cases	**Population Controls**	**GERD[3] Controls**	**Adjusted OR[1]**	**95% CI[2]**	**Adjusted OR[1]**	**95% CI[2]**
Total Adiponectin							
Quartiles[4] (μg/ml[6])							
<7.35	80	77	81	ref		ref	
7.36–10.55	63	76	88	0.83	(0.53, 1.33)	0.79	(0.50, 1.25)
10.56–15.41	82	76	75	1.13	(0.72, 1.77)	1.33	(0.84, 2.11)
>12.46	85	76	64	1.36	(0.83, 2.23)	1.96	(1.17, 3.27)
Continuous, Log-transformed	310	305	308	1.36	(0.97, 1.89)	1.66	(1.19, 2.32)
Adiponectin High MW[5]							
Quartiles[4] (μg/ml[6])							
<1.46	82	77	89	ref		ref	
1.46–2.53	74	76	77	0.95	(0.61, 1.50)	1.16	(0.74, 1.83)
2.54–4.00	69	76	66	0.92	(0.58, 1.45)	1.32	(0.82, 2.12)
>4.02	85	76	76	1.32	(0.80, 2.17)	1.65	(1.00, 2.73)
Continuous, Log-transformed	310	305	308	1.20	(0.96, 1.51)	1.33	(1.05, 1.68)
Adiponectin Low + Medium MW[5]							
Quartiles[4] (μg/ml[6])							
<2.75	72	77	87	ref		ref	
2.75–3.80	78	76	76	1.15	(0.73, 1.81)	1.33	(0.84, 2.10)
3.80–5.07	69	76	77	1.06	(0.66, 1.69)	1.25	(0.79, 1.99)
>5.07	91	76	68	1.56	(0.97, 2.53)	2.18	(1.33, 3.56)
Continuous, Log-transformed	310	305	308	1.44	(0.98, 2.11)	1.88	(1.28, 2.78)
Adiponectin Ratio High MW[5]/total							
Quartiles[4]							
<0.32	86	77	67	ref		ref	

	Counts			Cases vs. Population Controls		Cases vs. GERD[3] Controls	
	Cases	**Population Controls**	**GERD[3] Controls**	**Adjusted OR[1]**	**95% CI[2]**	**Adjusted OR[1]**	**95% CI[2]**
0.32–0.39	67	76	93	0.81	(0.51, 1.27)	0.58	(0.36, 0.91)
0.39–0.47	82	76	70	1.03	(0.66, 1.63)	0.92	(0.57, 1.48)
>0.47	75	76	78	0.98	(0.61, 1.57)	0.82	(0.50, 1.34)
Continuous, Log-transformed	310	305	308	1.22	(0.71, 2.09)	1.19	(0.68, 2.08)

[1] Adjusted OR (odds ratio): adjusts for sex, age, race/ethnicity and waist circumference

[2] CI: confidence interval

[3] GERD: Gastroesophageal reflux disease

[4] Quartiles are based on population control group

[5] MW= molecular weight

[6] µg/ml micro liters per milliliter

Table 3

Associations of adiponectin and Barrett's esophagus: stratified by GERD symptom frequency[3] for case vs. population controls

	Less than weekly[6]				At least weekly[7]			
	Case	**Control[9]**	**Adjusted OR[1]**	**95% CI[2]**	**Case**	**Control**	**Adjusted OR[1]**	**95% CI[2]**
Total Adiponectin interaction term Quartiles[4] (μg/ml[8])	<0.001							
<7.35	19	51	ref		61	26	ref	
7.36–10.55	14	51	0.67	(0.29, 1.55)	49	25	0.83	(0.42, 1.64)
10.56–15.41	9	60	0.39	(0.16, 0.99)	73	15	2.11	(1.00, 4.45)
>15.46	20	56	1.24	(0.52, 2.95)	65	20	1.56	(0.72, 3.37)
Continuous, Log-transformed	62	218	1.16	(0.62, 2.20)	248	86	1.68	(1.01, 2.80)
Adiponectin High MW[5] interaction term Quartiles[4] (μg/ml[8])	<0.001							
<1.46	20	48	ref		62	29	ref	
1.46–2.53	14	53	0.55	(0.24, 1.27)	60	23	1.18	(0.60, 2.32)
2.54–4.00	12	61	0.42	(0.18, 0.99)	57	15	1.72	(0.82, 3.63)
>4.02	16	56	0.84	(0.35, 2.04)	69	19	1.95	(0.89, 4.29)
Continuous, Log-transformed	62	218	0.98	(0.64, 1.51)	248	86	1.50	(1.04, 2.15)
Adiponectin Low + Medium MW[5] interaction term Quartiles[4] (μg/ml[8])	<0.001							
<2.75	16	56	ref		56	21	ref	
2.75–3.80	16	52	1.02	(0.45, 2.33)	62	24	0.91	(0.45, 1.85)
3.80–5.07	12	55	0.80	(0.33, 1.93)	57	20	1.16	(0.55, 2.43)
>5.07	18	55	1.57	(0.66, 3.72)	73	21	1.33	(0.62, 2.84)
Continuous, Log-transformed	62	218	1.52	(0.72, 3.21)	248	86	1.56	(0.87, 2.80)
Adiponectin Ratio High MW[5]/total interaction term Quartiles[4]	<0.001							
<0.32	19	48	ref		67	29	ref	
0.32–0.39	12	52	0.56	(0.24, 1.33)	55	24	0.95	(0.48, 1.86)
0.39–0.47	16	60	0.70	(0.31, 1.58)	66	15	1.95	(0.92, 4.11)
>0.47	15	58	0.73	(0.32, 1.69)	60	18	1.49	(0.70, 3.17)
Continuous, Log-transformed	62	218	0.66	(0.26, 1.67)	248	86	2.27	(0.96, 5.41)

[1] Adjusted OR (odds ratio): adjusts for sex, age, race/ethnicity and waist circumference

[2] CI: confidence interval

[3] GERD: gastroesophageal reflux disease

[4] Quartiles are based on population control group

[5] MW= molecular weight

[6] Reported frequency of GERD symptoms as less than weekly

[7] Reported frequency of GERD symptoms as weekly or more than weekly

[8] μg/ml= microliter per milliliter

[9] Note: Not all populations controls had GERD frequency data