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Associations of serum adiponectin and leptin with Barrett's esophagus

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Abstract

Background—Central adiposity is a risk factor for Barrett's esophagus (BE). Serum levels of adiponectin and leptin are deregulated in obese states and implicated as putative mediators in the pathophysiology of esophageal columnar metaplasia.

Aim—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 two 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 show that patients in the highest tertile of serum adiponectin had decreased odds of BE compared with screening colonoscopy controls (odds ratio (OR)=0.42, 95% Confidence Interval (CI)=0.22, 0.80)). This effect was more pronounced in males (OR=0.35, 95% CI=0.17, 0.74) compared to females (OR=0.71, 95%CI=0.17, 3.03).

In comparisons of BE cases to GERD controls, subjects in the highest tertile of serum adiponectin showed decreased odds of BE (OR=0.65, 95% CI 0.31, 1.36), however, this was not statistically

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significant. Patients in the highest tertile of serum leptin did not have significantly increased risk of BE in comparison to 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 association of leptin with odds of BE.

Conclusions—Serum adiponectin was inversely associated 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 further explored.

Keywords

adipokine; esophagus; epidemiology

Introduction

Obesity is a strong risk factor for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC)[1-4]. Being obese increases the odds of esophageal cancer approximately 1.5 fold in both sexes[5]. Obesity is now 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 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 elevated levels of circulating leptin and they exhibit leptin resistance. Leptin binds the leptin receptor at the cell surface and the signal is transduced intracellularly through the Janus kinase 2 (Jak2)/ 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, pro-inflammatory and mitogenic. Adiponectin is a protein encoded by the ADIPOQ gene and also secreted by the white adipose tissue. It circulates in three multimeric forms: low molecular weight (LMW), middle molecular weight (MMW) and high molecular weight (HMW) adiponectin. The adiponectin protein contains four 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 alpha mediated signaling[11, 12]. Adiponectin plays an important role in glucose flux and energy metabolism, upregulation 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 either shown no evidence of association with BE[14], or demonstrated a protective effect for LMW adiponectin[16]. Other studies have suggested that the effect of adipokines on esophageal metaplasia may be sex specific[17]. We sought to further clarify these relationships in a case-

control study comparing patients with BE to GERD controls and population controls. We hypothesized that serum leptin levels will be positively associated with increased risk of BE whereas increasing serum adiponectin will 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 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 which were defined as report of persistent reflux not relieved by adequate dose of proton pump inhibitor warranting further endoscopic evaluation. Diagnosis of GERD was established based on the assessment of patient's treating physician. pH probe testing was not used to establish 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 prior endoscopic exams, history of inflammatory bowel disease or colorectal cancer. In brief, we enrolled 135 patients with BE, 133 patients with GERD but no endoscopic or histological evidence of BE, and 1157 screening colonoscopy controls. This sample size was calculated based on assumption that at least 30% of cases will have elevated levels of serum adipokines, BMI, waist to hip ratio and other risk factors relevant to pathophysiology of BE and our goal to identify risk factors that increased odds of BE 2-4 fold. The study was approved by the Institutional Review Board of the Case Comprehensive Cancer Center and written informed consent was obtained on all participants.

Serum adiponectin and leptin

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

Statistical methods

Simple descriptive statistics were performed to describe the frequencies of risk factors among cases and controls. Univariate logistic regressions were completed to calculate ORs and the associated 95% CIs on all variables of interest. Multivariate regression analyses were conducted in order 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 highest tertiles to the lowest. Cutoff points for tertile

analysis of adiponectin and leptin were first determined separately for each sex for the entire study group. These sex-specific tertiles were then also 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 two-sided and p values less than 0.05 were considered significant. Statistical analyses were performed in 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. Waist to hip ratio of BE cases was significantly higher than that of screening colonoscopy controls. More female participants were recruited into both control groups compared to the BE case group. A higher proportion of non-white individuals were included among screening colonoscopy controls (see Table 1).

Total Adiponectin and risk of BE

Mean total adiponectin levels were not significantly different between BE cases and GERD controls [8.39 μg/mL (SD 4.18) vs. 8.82 μg/mL (SD 5.07), p=0.45]. Mean levels of serum adiponectin were statistically significantly lower in BE cases compared to screening colonoscopy controls [8.39 (SD 4.18) vs. 10.36 (SD 6.25) μg/mL, p=<0.001.

In tertile analysis of total adiponectin among BE cases and GERD controls, subjects in the highest tertile of serum adiponectin levels showed no statistically significant association with BE case status (ORa=0.65 (95% CI=0.31, 1.36)). When BE cases were compared to screening colonoscopy controls, subjects in the highest tertile of serum adiponectin did show a significantly decreased odds of BE (ORa=0.42 (95% CI=0.22, 0.80)). Details of these analyses are summarized in Table 2. Effects of sex on risk of BE in relation to serum adiponectin were considered. Association between adiponectin and BE in comparisons with screening colonoscopy group was statistically significant in males but not in females (Table 3). Including the interaction term of sex and adiponectin in modeling odds of BE was not statistically significant (p=0.90). Adiponectin showed an inverse association with BE case status and the strength of this association increased with rising serum levels of adiponectin suggesting a dose response relationship. This held true in sex specific analysis of BE cases with GERD controls in males but not among female participants (Table 4).

Leptin and risk of BE

Mean levels of serum leptin were lowest among BE cases and highest in screening colonoscopy controls [17.8 (SD 14.7) vs. 21.68 (SD 21.07) ng/mL, p=0.007].

In tertile comparisons of serum leptin among BE cases and GERD controls, subjects in the highest tertile of leptin did not show increased odds of BE (ORa=1.32, 95% CI=0.61, 2.88).

In comparisons of BE cases with screening colonoscopy controls, subjects in the highest tertile of serum leptin did not have increased odds of BE (ORa=1.57, 95%CI=0.81, 3.04).

Sex specific effects of leptin were further explored. Serum leptin did not show significant association with BE case status in either sex in comparisons with screening colonoscopy controls of GERD controls (Tables 3 and 4). There was a trend toward positive association of serum leptin and BE case status in females in analysis with screening colonoscopy controls and males in comparisons with GERD controls, however, this association was not statistically significant. The number of BE cases for this analysis was small questioning the validity of this analysis. The *p* values reported in tables 3 and 4 correspond to the test for linear trend when models are adjusted for age, sex, and race. Changing the models further to include an interaction term for gender and leptin did not show a significant association with presence of BE (p=0.09).

DISCUSSION

To understand the putative role of central obesity and its associated hormonal derangements we assessed the relationships of two serum adipokines with BE compared to two control groups. Consistent with our hypothesis, rising serum adiponectin showed an inverse association with BE and this effect was more pronounced in males. The observed associations of adiponectin with BE remained significant after adjustment of potential confounders such as age, sex, race and waist to hip ratio suggesting that this adipokine is strongly associated with BE and may play a biological role in the pathogenesis of esophageal columnar metaplasia. Contrary to our hypothesis, rising levels of serum leptin did not increase the odds of BE.

The protective effect of adiponectin observed in this study is biologically plausible and consistent with the findings of several other epidemiological[19-21] and molecular studies[22]. The role of adiponectin as an anti-proliferative factor has been recently studied in OE33 ECA cell lines. Adiponectin reduces leptin stimulated JAK2 activation and STAT3 transcriptional activity and increases protein-tyrosine phosphatase 1B (PTP1B) protein expression and its activity. Activation of PTP1B by adiponectin appears to downregulate leptin induced signaling and its pro-carcinogenic potential[23]. Increased adiponectin receptor expression and higher leptin receptor protein levels have been measured in areas of intestinal metaplasia vs. that of normal esophagus[24]. These findings emphasize the interplay of both adiponectin and leptin as regulators of cellular proliferation.

The lack of significant association of serum leptin with BE observed here was contrary to some reports published to date. This negative finding may reflect differences in case and control populations among various studies examining this subject. Recent analysis by Garcia et al[14] demonstrated that cases in the highest quintile of serum leptin had an 8 fold increased odds of BE (OR=8.02, 95% CI 2.79-23.07). In that study, analyses of leptin were also adjusted for medication use (PPI, NSAIDs) as well as *Helicobacter pylori* status. Rubenstein et al. described that leptin increased odds of BE approximately three fold in the highest tertile (OR= 3.25, 95% CI 1.29, 8.17)[25]. Both of these reports were from Veterans Affairs Medical Centers and the study populations were almost exclusively males. However,

similarly to findings of this study, Thompson et al [17] found that males in the highest tertile of leptin had no increased risk of BE. The Seattle study was conducted among non-Veterans and the demographics of their study group may be more representative of the general U.S. population and similar to those subjects enrolled in our study possibly yielding similar estimates of effect. It is also important to note that in our study serum leptin appeared to have strong positive association with BE in second but not third tertiles in comparisons with both colonoscopy and GERD controls. This was also true for sex specific analyses. In fact, analysis of BE and screening colonoscopy controls showed that in the second tertile the odds of BE were increased in males 2-3 fold (ORc=3.02, 95% CI 1.66, 5.49; ORa=2.21, 95% 1.11, 4.40)) and for females they were increased six to eight fold (ORc=8.45, 95% CI 1.92, 37.2; ORa=6.44, 95% CI 1.34, 31.1); estimates quite similar to those published in other studies[14, 16]. The overall trend of these associations may represent a ceiling effect where distribution of the leptin is skewed. In our further analysis of association of leptin with BMI, leptin levels appeared to plateau at the highest levels of BMI (Figure 1). If indeed the association of Leptin and BMI is non-linear, it provides a possible explanation to why odds ratios peaked in the second tertile and then appeared to decline in the third tertile. An observation like this could lead us to an erroneous conclusion that there is no association of leptin and BE case status when in fact there is.

Males have a higher distribution of metabolically active central fat compared to females and this may partly explain the higher prevalence of BE in males. Thus, our study as well as others[17] have performed subgroup analyses to explore sex specific associations of adipokines with BE. We did find that the protective effect of adiponectin was present in males but not in females, whereas there was no evidence of association with leptin in either subgroup. The number of females with BE in our study was small (n=27), leading to imprecise estimates of effect for both adipokines in this subgroup. In the only other study that included greater number of women[17] the authors did find a positive association between leptin and BE among females but did not find an association in males.

There are a few limitations to our study. A case-control design is susceptible to selection bias. This was partially controlled here by the prospective nature of this study. Selection bias was further minimized by recruitment of cases and both control groups from a similar target population. The BE case group included a small number of females, which did not allow for thorough examination of how sex mediated associations of interest. We were also unable to control for certain confounders that may contribute to risk of BE such as tobacco use, *Helicobacter pylori* status, dietary habits, presence of metabolic syndrome, diabetes and level of physical activity. Finally, the choice of our control groups could have introduced misclassification. Not all screening colonoscopy cases had an upper endoscopy performed and it is possible that there were undiagnosed BE cases among these controls. Prior studies have indicated that in individuals over 65 years of age, BE may be present in 16.7% of cases with 14.9% of those being asymptomatic[26]. However, misclassification would have attenuated our estimates only slightly given overall low prevalence of BE.

In summary, this study demonstrates that adiponectin has an inverse association with BE case status. The association was statistically significant in men when compared to colonoscopy controls but not GERD controls. Given that our results regarding the magnitude

of associations for serum adiponectin and leptin differ from other studies, performing a high quality metanalysis would be useful in order to obtain a better understanding of the relationship between these serum adipokines and BE case status. Further molecular and translational research will be needed to understand the specific role of adipokine signaling in BE. Future research efforts will need to determine whether interception of adipokine signaling pathways by upregulation of signaling or receptor activity could provide a therapeutic means of halting the metaplasia-dysplasia-carcinoma sequence or novel treatment targets for management of EAC.

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Abbreviations

BE	Barrett's esophagus
GERD	gastroesophageal reflux disease
OR	odds ratio
CI	confidence interval
EAC	esophageal adenocarcinoma
Jak 2	Janus kinase 2
STAT3	Signal transducer and activator of transcription 3
LMW	low molecular weight
MMW	middle molecular weight
HMW	high molecular weight
PTP1B	protein-tyrosine phosphatase 1B

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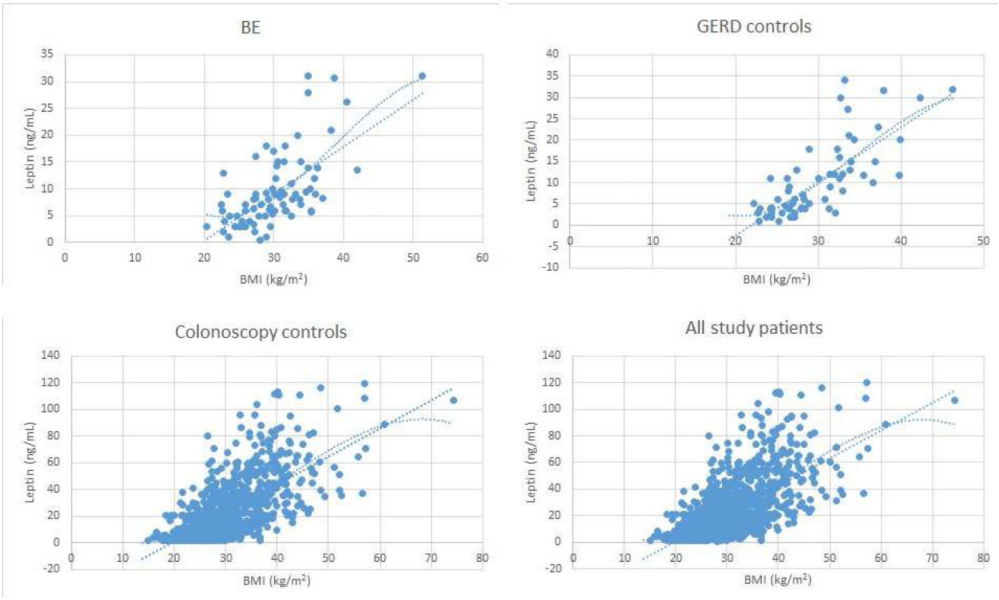

Figure 1.

Distribution of serum leptin in each study group and the entire study cohort. Two trend lines included are the linear trend line and polynomial trend line with 3 degrees of freedom.

Table 1

Demographic Variables by Study Group

	BE Cases	GERD Controls	Screening Colonoscopy Controls	p*	p**
Age (mean, SD)	63.7 (11.2)	56.4 (11.1)	54.6 (8.8)	<0.01	<0.01
Waist-to-hip ratio (mean, SD)	0.98 (0.06)	0.97 (0.07)	0.91 (0.09)	0.09	<0.01
Body Mass Index (mean, SD)	30.8 (5.7)	29.5 (5.6)	29.3 (6.9)	0.09	0.03
Gender (% female)	20.3%	40.0%	65.3%	<0.01	<0.01
Race				<0.01	<0.01
Caucasian	93.23%	82.96%	61.28%		
Other	6.77%	17.04%	38.72%		

*p-value of difference between BE and GERD controls

**p-value of difference between BE and colonoscopy controls

Table 2

Tertiles of Adiponectin and Leptin for BE cases compared to GERD Controls and Screening Colonoscopy Controls with adjustment for age, gender, race, and waist to hip ratio.

	Tertiles			
	1	**2**	**3**	**p (trend)**
BE cases vs. Colonoscopy controls				
Adiponectin				
Range				
Men	<5.33	5.33-8.75	>8.75	
Women	<7.62	7.62-12.92	>12.92	
Cases	36	52	45	
Controls	386	372	399	
ORc95%CI)†	1.0 (referent)	1.49 (0.95, 2.35)	1.20 (0.76, 1.92)	0.45
ORa (95%CI)‡	1.0 (referent)	0.98 (0.55, 1.74)	0.42 (0.22, 0.80)	0.006
Leptin				
Range				
Men	<5	5-12.24	>12.24	
Women	<13.65	13.65-30.72	>30.72	
Cases	20	63	50	
Controls	408	366	383	
ORc (95% CI)	1.0	3.51 (2.08, 5.92)	2.66 (1.55, 4.55)	0.001
ORa (95%CI)	1.0	2.70 (1.48,4.94)	1.57 (0.82, 3.04)	0.22
BE cases vs. GERD controls				
Adiponectin				
Range				
Men	<5.33	5.33-8.75	>8.75	
Women	<7.62	7.62-12.92	>12.92	
Cases	36	52	45	
Controls	48	46	41	
ORc (95%CI)	1.0 (referent)	1.50 (0.84, 2.71)	1.46 (0.80, 2.67)	0.22
ORa (95% CI)	1.0 (referent)	1.39 (0.70, 2.76)	0.65 (0.31, 1.36)	0.29
Leptin				
Range				
Men	<5	5-12.24	>12.24	
Women	<13.65	13.65-30.72	>30.72	
Cases	20	63	50	
Controls	39	46	50	
ORc (95% CI)	1.0 (referent)	2.67(1.38, 5.16)	1.94 (1.00, 3.79)	0.12
ORa (95% CI)	1.0 (referent)	2.72 (1.28, 5.74)	1.32 (0.61, 2.88)	0.66

†ORc = crude odds ratio

‡ORa = adjusted odds ratio

Table 3

Tertiles of Adiponectin and Leptin for BE cases compared to screening colonoscopy controls presented for each gender separately.

	Tertiles			
	1	**2**	**3**	**p (trend)**
Men (n=498)				
Adiponectin				
Range				
Men	<5.33	5.33-8.75	>8.75	
Cases	32	34	40	
Controls	136	131	125	
ORc95%CI)	1.0 (referent)	1.10 (0.64, 1.89)	1.36 (0.81, 2.30)	0.25
ORa (95%CI)	1.0 (referent)	0.70 (0.36, 1.38)	0.35 (0.17, 0.74)	0.005
Leptin				
Range				
Men	<5	5-12.24	>12.24	
Cases	18	45	43	
Controls	145	120	127	
ORc (95% CI)	1.0	3.02 (1.66, 5.49)	2.72 (1.50, 4.97)	0.001
ORa (95%CI)	1.0	2.21 (1.11, 4.40)	1.26 (0.61, 2.64)	0.62
Women (n=792)				
Adiponectin				
Range				
Women	<7.62	7.62-12.92	>12.92	
Cases	4	18	5	
Controls	250	241	274	
ORc (95%CI)	1.0 (referent)	4.66 (1.55, 14.0)	1.14 (0.30, 4.29)	0.97
ORa (95% CI)	1.0 (referent)	2.56 (0.74, 8.85)	0.71 (0.17, 3.03)	0.43
Leptin				
Range				
Women	<13.65	13.65-30.72	>30.72	
Cases	2	19	9	
Controls	259	245	261	
ORc (95% CI)	1.0 (referent)	8.45 (1.92, 37.2)	4.46 (0.96, 20.86)	0.11
ORa (95% CI)	1.0 (referent)	6.44 (1.34, 31.1)	5.21 (1.03, 26.18)	0.05

†ORc = crude odds ratio

‡ORa = adjusted odds ratio

Table 4

Tertiles of Adiponectin and Leptin for BE cases compared to GERD controls presented for each gender separately.

	Tertiles			
	1	**2**	**3**	**p (trend)**
Men (n=187)				
Adiponectin				
Range				
Men	<5.33	5.33-8.75	>8.75	
Cases	34	34	38	
Controls	27	28	26	
ORc95%CI)	1.0 (referent)	0.93 (0.45, 1.97)	0.90 (0.44, 1.82)	0.76
ORa (95%CI)	1.0 (referent)	0.92 (0.40, 2.10)	0.45 (0.19, 1.07)	0.07
Leptin				
Range				
Men	<5	5-12.24	>12.24	
Cases	18	47	41	
Controls	25	23	33	
ORc (95% CI)	1.0	2.84 (1.30, 6.22)	1.72 (0.81, 3.69)	0.30
ORa (95%CI)	1.0	2.18 (0.90, 5.26)	0.88 (0.35, 2.21)	0.58
Women (n=81)				
Adiponectin				
Range				
Women	<7.62	7.62-12.92	>12.92	
Cases	3	9	15	
Controls	23	12	19	
ORc (95%CI)	1.0 (referent)	5.62 (1.63, 19.3)	3.47 (0.75, 15.9)	0.04
ORa (95% CI)	1.0 (referent)	3.89 (0.96, 15.7)	1.93 (0.37, 9.97)	0.34
Leptin				
Range				
Women	<13.65	13.65-30.72	>30.72	
Cases	2	16	9	
Controls	14	23	17	
ORc (95% CI)	1.0 (referent)	4.87 (0.97, 24.4)	3.70 (0.69, 20.02)	0.22
ORa (95% CI)	1.0 (referent)	5.76 (0.95, 35.0)	4.42 (0.71, 27.43)	0.17

†ORc = crude odds ratio

‡ORa = adjusted odds ratio