Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

Role of serum adiponectin level in assessment of obese patients with Barrett's esophagus

Ayman M. EL Lehleh, Manal A. Ellaithy, Ahmed N. Zahran, and Naglaa S. Elabd

PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

Role of serum adiponectin level in assessment of obese patients with Barrett's esophagus

Ayman M. EL Lehleh[1], Manal A. Ellaithy[2], Ahmed N. Zahran[3], and Naglaa S. Elabd[1]

[1]Tropical Medicine Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt
[2]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt
[3]Hepatology and Gastroenterology Department, Shebin El-Kom Teaching Hospital, Menoufia, Egypt

ABSTRACT

Background: Obesity especially visceral obesity is an important independent risk factor for the development of gastro-esophageal reflux disease (GERD) and, Barrett's esophagus (BE). **Aim:** In this work, we aimed to evaluate serum adiponectin level in obese patients with GERD and Barrett's oesophagus as well as highlight its role in early predicting Barrett's oesophagus. **Materials and Method:** 120 participants with BMI ≥ 25 were involved in this case control study. They were grouped into Group I**:** 30 participants of coincided BMI, age and gender as obese controls; Group II: included 60 patients with GERD, and Group III**:** 30 patients with BE. All participants were subjected to clinical evaluation, Upper endoscope and serum adiponectin by ELISA. Biopsy with histopathological evaluation to confirm BE was done. **Results**: Significantly lower plasma adiponectin levels were detected in BE patients compared to GERD patients and the control group with significantly higher plasma adiponectin levels in GERD compared to controls. ROC analysis showed that AUC was 0.958 at a cut-off point ≤ 0.74, sensitivity and specificity were (90.0% and 95.0% respectively) for prediction of BE in GERD patients. Lower adiponectin levels were found in patients with large sliding hiatus hernia, long-segment Barrett as well as patients with high-grade dysplasia. Multivariate analysis displayed that adiponectin could be an independent predictor for BE. **Conclusion**: Obesity is a substantial risk for the development of GERD and BE. Adequate weight control is an important step for the prevention of BE. Additionally, adiponectin serum levels could be a reliable non-invasive biomarker for early prediction of BE.

Keywords: Adiponectin; Barrett's oesophagus; GERD; obesity

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/jcbr.2021.80400.1214

ARTICLE INFO

Article history

Receive: June 12, 2021
Revised: September 5, 2021
Accepted: October 9, 2021

Correspondence to

Naglaa Said Elabd, MD
Tropical Medicine Department,
Faculty of Medicine,
Menoufia University, Egypt
Tel.: 00201092304322
E-mail: naglaa_elabd@yahoo.com
Naglaa.alabd.12@med.menofia.edu.eg
ORCID ID: https://orcid.org/0000-0001-8786-0190

INTRODUCTION

Obesity has been defined by the World Health Organization (WHO) as an abnormal or excessive accumulation of fat that poses a health risk, and it is identified as one of today's most blatantly visible-yet-neglected public health issues, that has amounted to epidemic attributions. Obesity represents leading public health defiance (GBD Obesity Collaborators, 2017).

Obesity, particularly visceral obesity, have been thought about carefully as a significant independent risk factor for the development of GERD, Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC). The simplest explanation is that abdominal obesity promotes gastro–esophageal reflux by mechanical impact (Alexandre et al., 2014; Carrossini et al., 2021).

Gastro-esophageal reflux disease (GERD) is a categorical disease that displays itself in three diverse phenotypes that represent different disorders: non-erosive esophagitis, erosive esophagitis and Barrett's esophagus (BE) (Dent et al., 2005; Labenz, 2009). It has been reported that the pathogeneses of GERD, BE and cancer are multifactorial and complex (Boeckxstaens et al., 2014).

The prevalence of GERD is increasing around the world (Sharma et al., 2008). It is linked to poor quality of life besides lifestyle-related disorders

such as sleep disturbances. It has been found that this rise is most likely related to an increase in the prevalence of obesity worldwide (Roman and Pandolfino, 2010).

Existing evidence showed that obesity has also been associated with GERD complications, including BE development and esophageal adenocarcinoma (EAC). These develop as a result of a mismatch between harmful elements and the oesophagus's defensive mechanisms (Vaezi and Richter, 1996). Obesity is thought to raise the likelihood of BE by two and a half folds. Furthermore, researchers discovered that every ten-pound increase in weight increases the risk of BE by 10%, and every five-point increase in BMI increases the risk by 35% (Stein et al., 2005).

It has been found that abdominal visceral fat is metabolically active and increased the inflammatory cytokines, cardiovascular disease in addition to insulin resistance (Calabro and Yeh, 2008). Esophageal inflammation, Barrett's esophagus, and esophageal adenocarcinoma are all linked to dysregulation of inflammatory cytokines released from the adipose tissue (Ryan et al., 2011). Diverse types of adipose tissue possess different hormonal effects, over and above that EAC and Barrett's disease are more closely linked to visceral obesity than to general obesity (El-Serag et al., 2014).

Adiponectin is a 30 kDa protein that is secreted in large amounts by adipocytes. Low plasma levels of adiponectin have been linked to a raised risk of a variety of cancers including; colorectal cancer (CRC), gastric cancers (GC), breast, prostate, and endometrial (Kelesidis et al., 2006). Moreover, most cases of EA are thought to be caused by Barrett's esophagus (BE), a premalignant metaplastic syndrome that develops in the presence of chronic gastroesophageal reflux (Engel et al 2003).

Consequently, attention is paid to study BE not only because patients diagnosed with BE are at high risk of developing EAC, but also because of the possibility that modifying behavioral risk factors for BE might be an effective method of preventing the development of EAC. So this work aimed to study serum adiponectin levels in obese patients with Barrett esophagus (BE) and to highlight its role in the early prediction of Barrett's esophagus besides the assessment of its relation with the clinic-pathological and endoscopic finding in these patients.

PATIENTS AND METHODS

This case control study included one hundred and twenty participants. They were selected with BMI ≥ 25. Patients and controls were chosen from the Tropical Medicine Department Faculty of Medicine, Menoufia University Hospital and Shebin El-Kom Teaching Hospital between October 2018 to April 2020. Laboratory investigations were completed in Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Menoufia University. Patients were grouped into one of the three groups: Group I included 30 obese persons without GERD as obese control. They were selected from patients presented with upper GIT symptoms or atypical manifestations of GERD with no Gastro-esophageal reflux finding in upper endoscopy or patients who undergo endoscopic management of obesity or pre-operative assessment before bariatric surgery. Group II comprised 60 obese patients with GERD. Diagnosis of GERD was done by the history of typical or atypical reflux symptoms and confirmed by the characteristic features in upper GIT endoscopy. Group III comprised 30 obese patients with Barrett's esophagus. Barrett's esophagus was diagnosed by characteristic endoscopic findings and confirmed by tissue biopsies with histopathological evaluation. The sample size was determined according to Greer et al. 2015 who revealed that adiponectin level was elevated in BE cases than GERD patients and healthy control with an adjusted odds ratio (1.39 [0.70 – 2.76] and 0.65 [0.31 – 1.36]) for second and third tertiles of adiponectin level respectively and with p-value 0.29, at a power 80%, alpha error 0.05 and control to case ratio 2:1, the estimated sample size was 60 GERD patients as a control group and 30 BE cases as a study group as well as 30 subjects as a healthy control

Participants included in this study were selected as specified by the following criteria: BM ≥ 25 with or without GERD provided that diagnosis confirmed by esophago-gastro- duodenoscopy, additionally, histopathological assessment of

tissue biopsies were performed for patients with suspicious Barrett's esophagus. Patients with previous gastroesophageal surgery, previous gastroesophageal cancer, patients with Inflammatory GI diseases that could be associated with low serum adiponectin level such as acute pancreatitis and inflammatory bowel diseases or autoimmune diseases as well as patients with malignancies anywhere in the body were excluded. Additionally, patients who received medical treatment with anticoagulants, statins, fibrates, nicotinic acid and acipimox that could affect serum adiponectin levels also were excluded.

For all participants, history of epigastric pain, heart burn, regurge, nausea or vomiting, postprandial fullness and atypical manifestations of GERD including dysphagia, night shocking, reflux cough and reflux asthma were assessed. Furthermore, drug history, history of smoking, family history of GERD or Barrett's esophagus were evaluated. Together with detailed clinical evaluation including estimating anthropometric measurements included body mass index (BMI), waist circumference, hip circumference, waist/ hip ratio and mid-arm circumference. Imaging valuation was performed for all participants by abdominal ultrasound. Laboratory assessment including, complete blood count, liver function tests, serum creatinine, fasting blood sugar, and lipid profile was estimated. Serum adiponectin was assessed by ELISA. Upper endoscopy was done for all participants, together with histopathological evaluation was done for patients suspected as Barrett's esophagus patients.

Ethical Approval: For all participants, an explanation about the study was provided together with informed consent were obtained from each one before enlisted in the study. The study was affirmed by the Faculty of Medicine, Menoufia University ethical committee (6/2018TROP5) and according to the Helsinki Declaration.

Serum adiponectin assessment: This assay employs the quantitative sandwich enzyme immunoassay technique by human total adiponectin / Acrp 30 Immunoassay kits provided by Sunred, China Catalogue No 201-12-1551. Blood samples were obtained in the morning after 12 hours of fasting from patients of all examined groups and controls. Blood serum was obtained after 15 minutes of clotting and centrifugation at 2000 rpm for 10 minutes. Serum was removed and stored frozen at –20°C. Adiponectin concentrations were measured with ELISA (R&D Systems, USA).

Endoscopic evaluation: Endoscopy was done by a skilled endoscopist with the patient in the left lateral position and the detailed clinical findings during the endoscopy procedure were noted in a pre-designed sheet. Grading of GERD was done according to The Loss Angelos (LA) classification (Ou et al., 2011). Four–quadrant biopsies at 2cm intervals were obtained from suspected Barrett lesions for histopathological examination to confirm diagnosis of Barrett's esophagus. Lesions of Barrett's esophagus were graded into islands of columnar extension, ultrashort segment Barrett's, short-segment Barrett's and long-segment Barrett's (Choe et al., 2016).

Statistical analysis

Data were represented as Mean ± standard deviation. The Kolmogorov-Smirnov was used to verify the normality of the distribution of variables, Comparisons between groups for categorical variables were assessed using the Chi-square test (Fisher or Monte Carlo). ANOVA test was utilized to compare the three studied groups and followed by Post Hoc test (Tukey) for pairwise comparison. Kruskal-Wallis test was used to compare different groups for abnormally distributed quantitative variables and followed by Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. The significance of the obtained results was judged at P-value < 0.05. These analyses were done using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

RESULTS

This case-control study was carried out on 90 patients, they were 48 males (53.3%) and 42 females (46.7%) with ages ranging from 27 to 64 years together with thirty obese patients of

matched age, sex and BMI as obese controls. Patients and controls were grouped into one of 3 groups: Group I composed of 30 obese controls, were 17 (56.7%) males and 13 (43.3%) females with a mean ± SD age of 39.3 ± 9 years, and Group II comprised 60 patients with GERD documented by upper endoscopy including 31 (51.7%) males and 29 (48.3%) females age of 42.4 ± 8.3 years, and Group III included 17 (56.7%) males and 13 (43.3%) females age of 43.5 ± 9.1 years (Table 1).

Clinically, we noticed that there was a statistically significant difference among the three studied groups regarding the symptoms suggestive of gastro-esophageal reflux disease; heart burn and regurge. Such symptoms were absent in obese controls while in GERD and Barrett groups were nearly similar. Epigastric pain was non-significantly different among the three groups (P = 0.407). Additionally, we observed that the atypical manifestations of reflux including night shocking, dysphagia, reflux asthma, reflux cough, and hoarseness of voice did not statistically differ among the three studied groups. Also, history of diabetes mellitus was significantly more frequent in GII (Table 1)

Regarding anthropometric measurements, BMI and mid-arm circumference did not show statistical differences among the three studied groups (p = 0.766 and 0.236 respectively), whereas waist/hip ratio was considerably higher in Barrett's esophagus patients (P = 0.036) (Table 1)

Basic laboratory investigations were presented in Table 2. Upper endoscopy showed that grading of GERD, the presence of LES incompetence & the presence of hiatus hernia were not different between GERD and Barrett's patient groups (P = 0.903, 0.055 and 0.894 respectively) (Figures 1A, 1B and 1C). The endoscopic grading of Barrett's patients showed that 40% had short-segment Barrett's (Figure 1D). Moreover, histopathological assessment displayed 70% of these patients were BE negative for dysplasia (figure 2A).

Serum adiponectin levels displayed a statistically significant difference among the three studied groups with the highest values in obese patients with GERD, in addition, the lowest levels were present in obese patients with Barrett's esophagus as shown in Figure 2B.

ROC curve analysis revealed that adiponectin at cut off > 3.6 has sensitivity, specificity of 50% and 86.67% with AUC 0.849 for predicting GERD in obese patients (Table 3, figure 2C). Additionally, ROC curve analysis to explore the role of adiponectin for predicting Barrett esophagus in obese patients with GERD revealed that adiponectin at cut off level ≤ 0.74 has sensitivity, specificity of 90% and 95% with AUC 0.958, additionally, PPV and NPV of 90% and 95% (Table 3, Figure 2D).

In obese patients with GERD, there was no significant relation between serum adiponectin level and gender, history of DM, liver echogenicity, the grade of GERD (Figure 3A), LES (lower esophageal sphincter) incompetence or hiatus hernia. In BE patients (group III), lower adiponectin level was significantly linked with the existence of large sliding hiatus hernia, long-segment Barrett in endoscopy as well as patients with high-grade dysplasia in histopathology (P = 0.048, < 0.001, < 0.001, respectively) as shown in table 4 and figures 3B, 3C and 3D, with no significant relations found regarding gender, liver echogenicity, the grade of GERD, the existence of LES incompetence or hiatus hernia.

For the parameters influencing Barrett esophagus *v.* GERD in obese patients, the univariate and multivariate logistic regression analysis revealed that, with the univariate test, FBS p = 0.018 OR 1.023 (1.004-1.042) and adiponectin p<0.001 OR 0.004 (0.010–0.189) could be meaningful in disease prediction, whilst, in multivariate analysis, adiponectin level p = 0.001 OR 75.012 (5.641-997.459) could be an independent predictor for Barrett esophagus (Table 5).

DISCUSSION

Obesity particularly the visceral type is considered to be one of the substantial independent risk factors for the evolution GERD and its associated complications (Alexandre et al., 2014). Likewise, it is intelligible that the existence of obesity ultimately enhances the risk of related comorbidities like dyslipidemia, diabetes, insulin resistance, hypertension, and

Table 1. Comparison between the three studied groups according to clinical data (history, general and local examination)

	Group I (n = 30)	Group II (n = 60)	Group III (n = 30)	Test of sig.	p
Gender					
Male	17 (56.7%)	31 (51.7%)	17 (56.7%)	χ^2=0.302	0.860
Female	13 (43.3%)	29 (48.3%)	13 (43.3%)		
Age (years)					
Mean ± SD.	39.3 ± 9	42.4 ± 8.3	43.5 ± 9.1	F =1.956	0.146
Median (Min. – Max.)	38 (25 – 56)	42.5 (27 – 63)	44 (28 – 64)		
Regurge	0 (0%)	37 (61.7%)	18 (60%)	χ^2=33.869*	<0.001*
Heart burn	0 (0%)	54 (90%)	25 (83.3%)	χ^2=77.468*	<0.001*
Epigastric pain	7 (23.3%)	22 (36.7%)	11 (36.7%)	χ^2=1.800	0.407
Atypical manifestations of GERD					
Night shocking	3 (10%)	6 (20%)	3 (10%)	χ^2=3.622	MCp=0.993
Dysphagia	1 (3.33%)	1 (1.66%)	0 (0%)		
Reflux asthma	0 (0%)	1 (1.66%)	0 (0%)		
Reflux cough	4 (13.33%)	5 (8.33%)	3 (10%)		
Hoarseness of voice	5 (16.66%)	4 (6.66%)	2 (6.66%)		
History of DM					
No	20 (66.7%)	25 (41.7%)	20 (6.77%)	χ^2=7.552*	0.023*
Yes	10 (33.3%)	35 (58.3%)	10 (33.3%)		
History of smoking	11 (9.2%)	29 (24.2%)	15 (12.5%)	χ^2=1.376	0.503
BMI (kg/m²)					
Mean ± SD.	32.6 ± 5.20	32.7±4.9	32 ± 4.5	F=0.267	0.766
Median (Min. – Max.)	32.3 (25.4 – 42.7)	31.6 (25.8 – 43.1)	30.2 (25.9 – 42.5)		
Waist/ Hip Ratio					
Mean ± SD.	1.26 ± 0.34	1.46 ± 0.37	1.39 ± 0.29	F=3.413	0.036*
Median (Min. – Max.)	1.22(0.88 – 2.30)	1.45(0.80 – 2.40)	1.37 (0.92 – 1.85)		
Mid arm circumference (cm)					
Mean ± SD.	35.1 ± 6.7	37.3 ± 6	36.6 ± 4.7	F=1.460	0.236
Median (Min. – Max.)	34.3 (28.4 – 61)	37 (28 – 59)	35.5 (29 – 44.5)		
Abdominal contour					
Normal	17 (56.7%)	28 (46.7%)	19 (63.3%)	Not applicable	
Diffuse abdominal enlargement with full flanks	13 (43.3%)	32 (53.3%)	11 (36.7%)		
Umbilicus shape					
Normal	19 (63.3%)	33 (55%)	22 (73.3%)	Not applicable	
Sunken	11 (36.7%)	27 (45%)	8 (26.7%)		
Stria alba					
Absent	21 (70%)	40 (66.7%)	23 (76.7%)	Not applicable	
Present	9 (30%)	20 (33.3%)	7 (23.3%)		
Liver size					
Average size	21 (70%)	43 (71.7%)	23 (76.7%)	Not applicable	
Hepatomegaly	9 (30%)	17 (28.3%)	7 (23.3%)		
Spleen size					
Average size	28 (93.3)	53 (88.3)	28 (93.3)	Not applicable	
Splenomegaly	2 (6.7)	7 (11.7)	2 (6.7)		

BMI: body mass index, χ^2: Chi-square test, MC: Monte Carlo, F: F for ANOVA test, p: p-value for comparing among the studied groups, *: Statistically significant at $p < 0.05$

others (Reaven, 2002). The collection of the aforementioned pathologies is generally known as metabolic syndrome or syndrome X (Reaven, 1992). Adiponectin is a 30 KDa protein secreted from adipocytes. It was found that depressed systemic levels of adiponectin were linked with a higher risk of multiple cancers (Kelesidis et al., 2006; Fadel et al., 2020). Adiponectin is expressed fundamentally in white adipose tissue and as stated by some reports in brown adipose tissue as well (T37i brown adipocyte cell line) (Viengchareun et al., 2002).

Table 2. Comparison between the three studied groups according to laboratory and ultrasound finding

	Group I (n = 30)	Group II (n = 60)	Group III (n = 30)	Test of sig.	p
Hemoglobin concentration (g/dl)					
Mean ± SD.	12.6 ± 1.2	12.5 ± 1.6	12.3 ± 1.5	F=0.307	0.736
Total leucocyte count (x10^2)					
Mean ± SD.	56.1 ± 9.4	60 ± 11	61 ± 10.4	F=1.888	0.156
Platelet count (x10^3)					
Mean ± SD.	219.8 ± 27.6	221.7 ± 30.5	228.5 ± 27.4	F=0.782	0.460
Alanine aminotransferase (U/L)					
Mean ± SD.	29 ± 14.8	30.5 ± 8.6	26.4 ± 17.4	F=0.972	0.381
Aspartate aminotransferase (U/L)					
Mean ± SD.	28.4 ± 10.6	29.7 ± 11.8	23.8 ± 13.7	F=2.392	0.096
AST (U/L) / ALT (U/L)					
Mean ± SD.	1.1 ± 0.3	1 ± 0.3	0.9 ± 0.2	F=1.237	0.294
Fasting blood sugar					
Mean ± SD.	115.3 ± 36.8	124 ± 37.7	104.4 ± 25.5	F=3.203*	0.044*
Sig. bet. grps	p_1=0.509 ,p_2=0.446 ,p_3=0.035*				
Total cholesterol (mg/dl)					
Mean ± SD.	216.3 ± 19.4	210.8 ± 20.4	212.4 ± 15.4	F=0.840	0.434
Triglycerides (mg/dl)					
Mean ± SD.	157.4 ± 18.9	160 ± 15.8	166.6 ± 15.2	F=2.530	0.084
Serum Adiponectin level					
Mean ± SD.	4.17 ± 9.85	22.4 ± 25.1	0.52 ± 0.52	H=58.838*	<0.001*
Median (Min. – Max.)	0.4 (0.16 – 42.4)	8.6 (0.41 – 75.5)	0.4 (0.15 – 2.53)		
Sig. bet. grps	p_1<0.001*,p_2=0.201,p_3<0.001*				
Liver echogenicity					
Normal	7 (23.3%)	5 (8.3%)	6 (20%)	χ^2=4.541	MCp=0.117
Bright	23 (76.7%)	55 (91.7%)	24 (80%)		
Liver size					
Normal	17 (56.7%)	32 (53.3%)	18 (60%)	χ^2=0.372	0.830
Hepatomegaly	13 (43.3%)	28 (46.7%)	12 (40%)		
Gall bladder wall					
Average	21 (70%)	42 (70%)	18 (60%)	χ^2=1.026	0.599
Thick	9 (30%)	18 (30%)	12 (40%)		
Gall bladder stone (s)					
Absent	22 (73.3%)	43 (71.7%)	22 (73.3%)	χ^2=0.042	0.979
Present	8 (26.7%)	17 (28.3%)	8 (26.7%)		
Size of spleen					
Normal	27 (90%)	53 (88.33%)	28 (93.33%)	χ^2=0.507	MCp=0.921
Splenomegaly	3 (10%)	7 (11.67%)	2 (6.67%)		

χ^2: Chi-square test FE: Fisher Exact, MC: Monte Carlo, F: F for ANOVA test, Pairwise comparison groups were done using Post Hoc Test (Tukey), p: p-value for comparing between the studied groups, p_1: p-value for comparing between Group I and Group II, p_2: p-value for comparing between Group I and Group III, p_3: p-value for comparing between Group II and Group III, *: Statistically significant at $p < 0.05$

Table 3. Agreement (sensitivity, specificity) for Adiponectin level to diagnose Obese patients with GERD and Barrett's esophagus patients

Adiponectin level	AUC	P	95% C.I		Cut off#	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Level 1	0.849	<0.001*	0.756	0.942	>3.60	50.0	86.67	88.2	46.6
Level 2	0.958	<0.001*	0.917	1.0	≤0.74	90.0	95.0	90.0	95.0

Level 1: Agreement (sensitivity, specificity) for Adiponectin level to diagnose Obese patients with GERD patients (group III) (n = 60) from control (n = 30). Level 2: Agreement (sensitivity, specificity) for Adiponectin level to diagnose Obese patients with Barrett's esophagus (group III) (n = 30) from Obese patients with GERD patients (group II) (n = 60). AUC: Area Under a Curve, p-value: Probability value, CI: Confidence Intervals, NPV: Negative predictive value, PPV: Positive predictive value, *: Statistically significant at $p < 0.05$, #Cut off was choose according to Youden index

Table 4. Comparison of adiponectin levels according to gender, history of DM, US liver finding, endoscopic finding, and histopathological finding in group III (n = 30)

	N	Adiponectin level			Test of Sig.	P
		Min. – Max.	Mean ± SD.	Median		
Gender						
Male	**17**	0.15 – 2.53	0.58 ± 0.63	0.36	U=103.0	0.773
Female	**13**	0.18 – 1.36	0.43 ± 0.31	0.37		
DM						
No	**20**	0.16 – 1.78	0.50 ± 0.41	0.37	U=86.0	0.559
Yes	**10**	0.15 – 2.53	0.54 ± 0.71	0.35		
Liver echogenicity						
Normal	**6**	0.22 – 0.65	0.41 ± 0.17	0.41	U=66.0	0.781
Bright	**24**	0.15 – 2.53	0.54 ± 0.57	0.34		
Liver size						
Normal	**18**	0.22 – 2.53	0.68 ± 0.61	0.44	U=39.0*	0.003*
Hepatomegaly	**12**	0.15 – 0.46	0.27 ± 0.11	0.25		
GERD grading						
Class A	**8**	0.29 – 0.65	0.42 ± 0.11	0.41	H=3.015	0.222
Class B	**16**	0.16 – 2.53	0.65 ± 0.67	0.35		
Class C	**6**	0.15 – 0.46	0.28 ± 0.12	0.26		
LES incompetence						
No	**1**	0.36			U=14.0	1.000
Yes	**29**	0.15 – 2.53	0.52 ± 0.52	0.37		
Hiatus hernia						
No	**15**	0.23 – 2.53	0.71 ± 0.67	0.43	H=6.084*	0.048*
Small sliding	**9**	0.16 – 0.72	0.35 ± 0.18	0.32		
Large sliding	**6**	0.15 – 0.46	0.27 ± 0.12	0.24		
Endoscopic findings of Barrett esophagus						
Islands of columnar extension	**4**	0.74 – 2.53	1.60 ± 0.75	1.57	H=26.323*	<0.001*
Ultrashort segment Barrett	**6**	0.46 – 0.72	0.55 ± 0.11	0.51		
Short segment Barrett	**12**	0.28 – 0.45	0.35 ± 0.06	0.34		
Long segment Barrett	**8**	0.15 – 0.23	0.19 ± 0.03	0.19		
Histopathology						
Negative for dysplasia	**21**	0.16 – 1.78	0.48 ± 0.39	0.37	H=16.891*	<0.001*
Low – grade dysplasia	**6**	0.18 – 0.74	0.39 ± 0.22	0.37		
High – grade dysplasia	**3**	0.15 – 0.20	0.17 ± 0.03	0.16		

U: Mann Whitney test, H: H for Kruskal-Wallis test, p: p-value for the association between different categories, *: Statistically significant at p < 0.05

Table 5. Univariate and multivariate logistic regression analysis for the risk factors of development of Barrett's esophagus in obese patients with GERD

	Univariate		#Multivariate	
	p	OR (95%C.I)	p	OR (95%C.I)
Gender (male)	0.654	1.223(0.506 – 2.955)		
Age (years)	0.534	1.017(0.965 – 1.070)		
Waist/ Hip Ratio	0.362	0.543(0.146 – 2.019)		
Mid arm circumference (cm)	0.589	0.978(0.902 – 1.060)		
FBS	**0.018***	1.023(1.004 – 1.042)	0.093	1.053(0.991 – 1.118)
Total Cholesterol (mg/dl)	0.700	1.005(0.981 – 1.028)		
TGs (mg/dl)	0.067	1.029(0.998 – 1.061)	0.054	0.910(0.827 – 1.002)
GERD grading	1.000	1.0(0.554 – 1.805)		
LES incontinence	0.080	6.510(0.799 – 53.056)	0.886	0.371(0.0 – 297298.6)
Hiatus hernia				
No				
Small sliding	0.758	0.853(0.309 – 2.349)		
Large sliding	0.657	0.771(0.245 – 2.426)		
Adiponectin level	**<0.001***	**0.044(0.010 – 0.189)**	**0.001***	**75.012(5.641 – 997.459)**
History of Smoking	0.765	1.143 (0.475-2.748)	-	-

OR: Odd`s ratio, B: Unstandardized Coefficients, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit, #: All variables with, p<0.05 was included in the multivariate, *: Statistically significant at p < 0.05

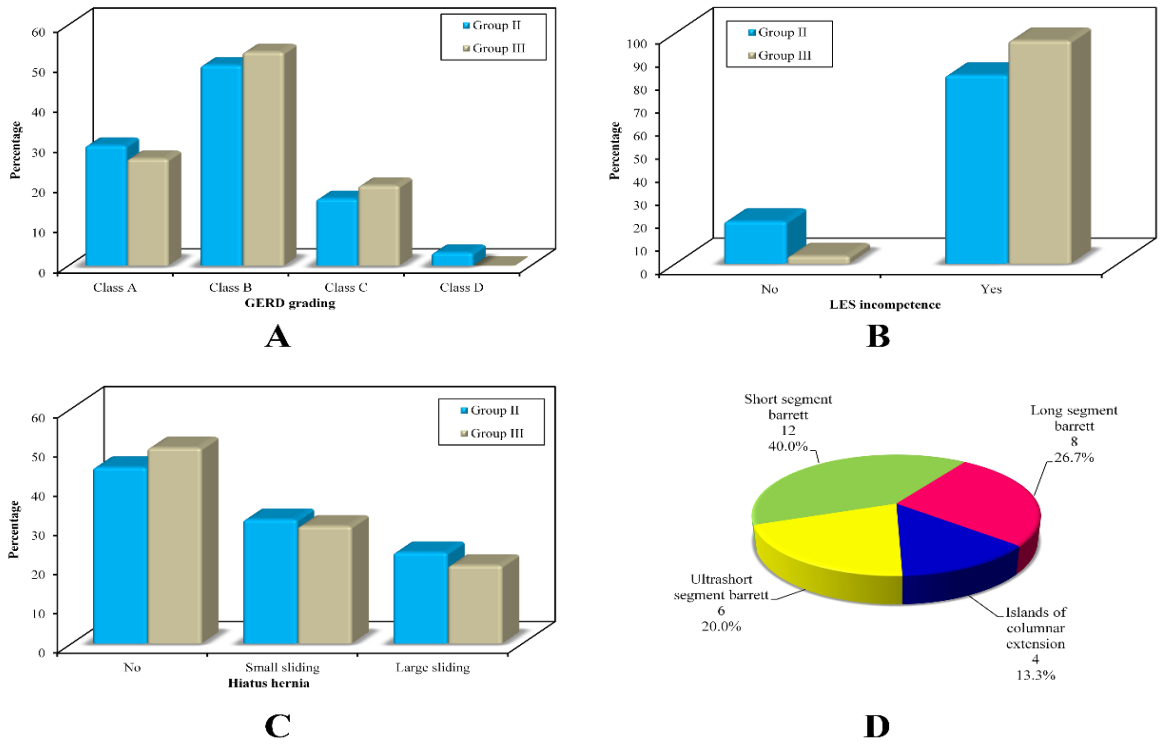

Figure 1. Comprison of different clijical characteristic of patients groups. A: Comparison between the two patient groups according to GERD grading, B: Comparison between the two patient groups according to LES incompetence, C: Comparison between the two patient groups according to the presence of Hiatus hernia, D: Endoscopic findings (Barrett grading) in obese patients with Barrett esophagus (n=30)

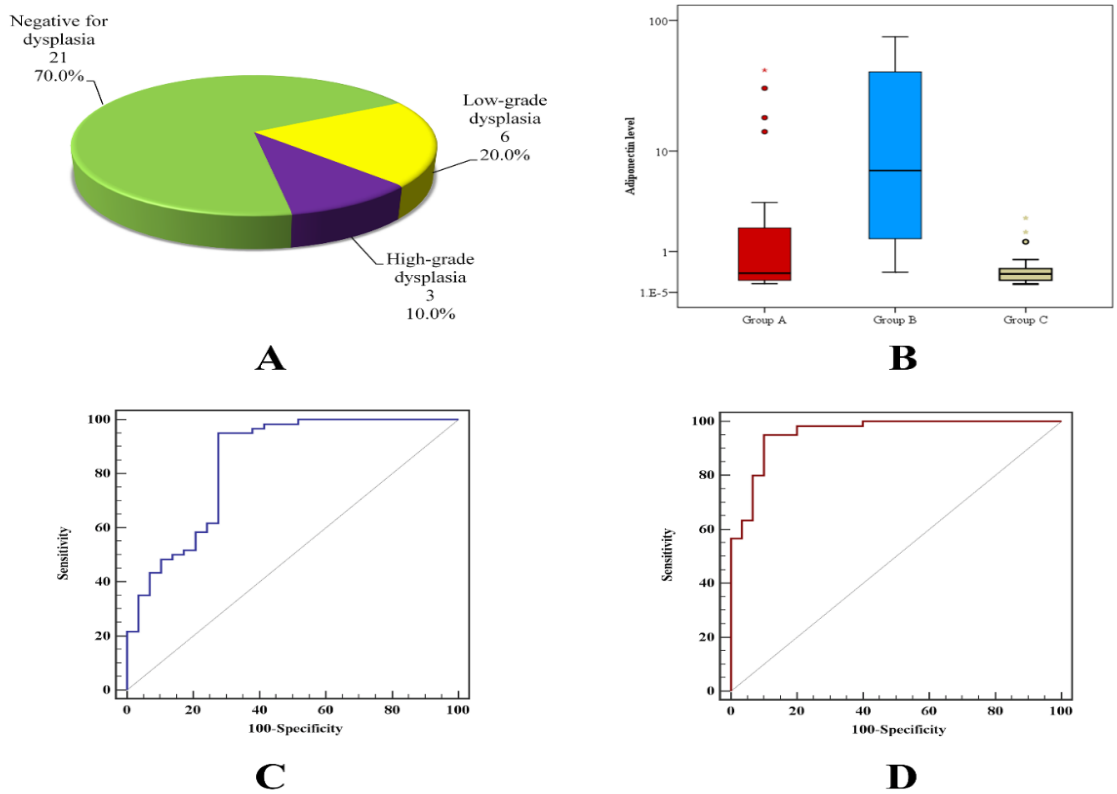

Figure 2. Comparing histopathological features of patients groups. A: Distribution of the studied cases according to histopathological finding in group III (Obese patients with Barrett's esophagus) (n = 30), B: Comparison between the three studied groups according to serum Adiponectin level, C: ROC curve for Adiponectin level to diagnose obese patients with GERD (n = 60) from obese control (n = 30), D: ROC curve for Adiponectin level to diagnose obese patients with Barrett's esophagus (group III) (n = 30) from obese patients with GERD (group II) (n = 60)

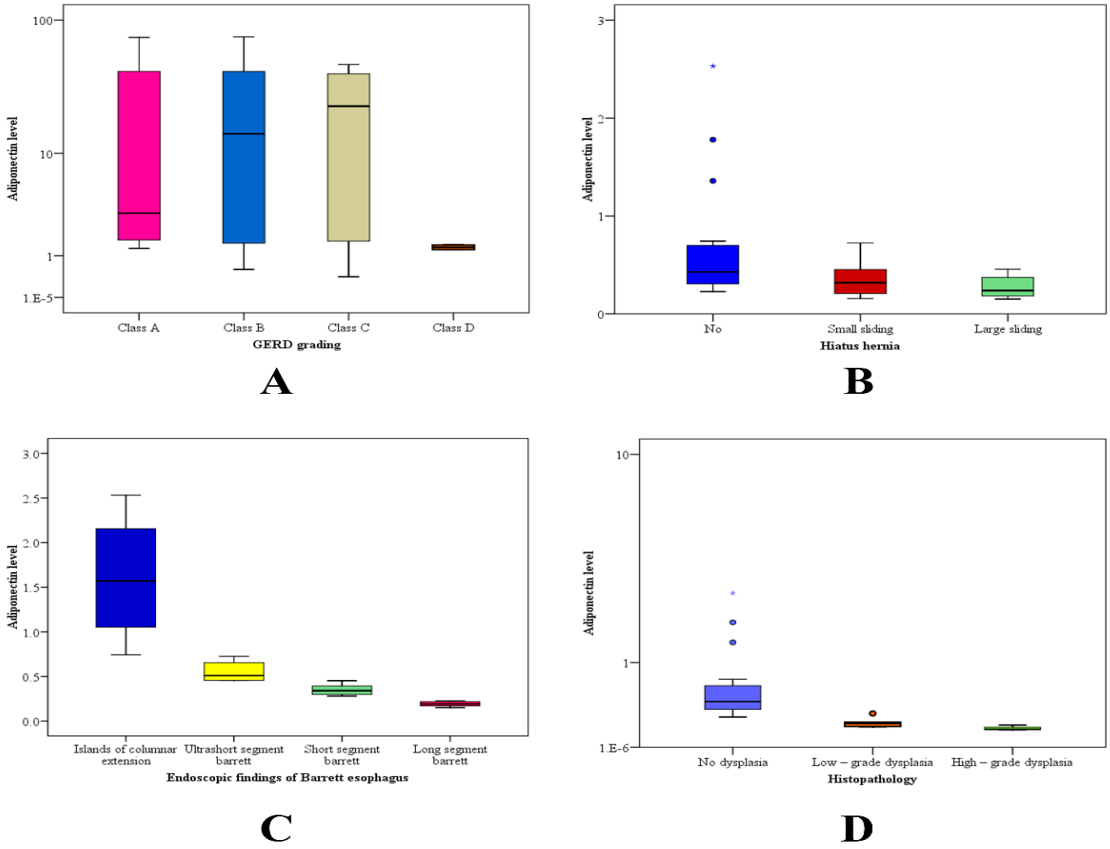

Figure 3. Comparing levels of adiponectin with different clinical features. A: Relation between adiponectin level with GERD grading in group II (n= 60), B: Relation between adiponectin level with the presence of Hiatus hernia in group III (n= 30), C: Relation between a level with Barrett grading in group III (n= 30), D: Relation between Adiponectin level with histopathological finding in group III (n= 30)

A number of hormonal as well as environmental factors are involved in the regulation of adiponectin gene. Adiponectin gene expression in white adipose tissue is reduced by β-adrenergic agonists glucocorticoids, and TNF-α (tumour necrosis factor α) and elevated by IGF-1 (insulin-like growth factor 1), cold exposure, leanness, and, adrenalectomy (Fasshauer et al., 2002; Makimura et al., 2002). In this study, we focused on investigating serum adiponectin level in obese patients with Barrett esophagus and assessing its relation with the clinic-pathological and endoscopic findings in these patients.

In the current study, we noted that there was no significant difference between the three studied groups regarding BMI, waist, hip or mid-arm circumferences. Whereas mean waist/hip ratio in BE group displayed significantly higher values than in the other groups. These findings suggest that BMI is the crude measure of adiposity that does not reflect fat distribution within the body. Previous data support our findings. For example, Edelstein et al. (2007) reported that central obesity parameters were strongly associated with a high risk of BE, whereas BMI influence was weaker. Additionally, El-Serag et al. (2005) found that the visceral adipose tissue, defined by CT scan, was linked with a higher risk of Barrett esophagus.

As it generates metabolically active pro-inflammatory cytokines, visceral fat has been thought about to be the compartment that takes part in the systemic effects of obesity. Existing evidence displayed that liposuction of subcutaneous fat had no effect on cardiac risk factors, whilst surgical removal of intra-abdominal adipose tissue improves glycemic control markers dramatically (Moayyedi, 2008). Furthermore, as compared to BMI, central adiposity markers (including waist circumference as well as waist-hip ratio) are more strongly linked to obesity-associated

disorders such as myocardial infarction (MI) and colorectal cancer (Yusuf et al 2005; Russo et al 1998).

We displayed noteworthy outcomes, where serum adiponectin levels in our study showed a statistically considerable difference between the three studied groups with the highest values were detected in obese patients with GERD compared to controls and BE patients. Numerous researches have illustrated similar results concerning GERD patients (Almers et al., 2015), (Greer et al., 2015) and (Al-Khalidy, 2018).

Higher adiponectin levels in GERD may be accountable for the aberrant esophageal mucosa healing that derive metaplasia and BE (Mokrowiecka et al., 2012). Another research exhibited that visceral fat increases the levels of inflammatory cytokines and adiponectin, which may raise the risk of GERD (Nam et al., 2015). As a result, a high adiponectin level in patients with GERD could protect them from Barrett's esophagus (Rubenstein et al., 2009).

In the present study, considerably lower serum adiponectin levels were noted in obese BE patients compared to obese patients with GERD, additionally, serum adiponectin levels were significantly lower than obese controls. Serum hypoadiponectinaemia in BE was reported in previous studies (Thompson et al., 2010; Mokrowiecka et al., 2012; Rafat et al., 2018). Additionally, in a former small study, authors found that low plasma levels of adiponectin are associated with an increased risk of Barrett's esophagus among patients undergoing upper endoscopy (Rubenstein et al., 2008).

It was formerly reported that low adiponectin levels have also been associated with an increased risk of several diverse types of cancer. Moreover, adiponectin receptors are expressed in the esophageal mucosa, and adiponectin has been displayed to induce apoptosis in a cell line of cancer esophagus (Konturek et al., 2008).

A variety of epidemiological and experimental studies back up adiponectin's role in cancer pathophysiology. A review article on adiponectin's relationship with cancers such as endometrial, gastric, colorectal cancers acute myelogenous leukemia, breast, and prostate was published by Kelesidis et al. (2006). Reduced adiponectin levels were linked to an increased risk of cancer in all instances.

On the other hand, these results disagree with that reported by Garcia et al. (2014) who concluded in a former case control study that BE was associated with statistically non-significant lower adiponectin levels than controls. This difference can be attributed to the difference in the population samples. In their study control group included patients who were eligible for screening colonoscopy and agreed for an EGD at the same time as their colonoscopy in addition to including BE patients and controls with any BMI. In the current study, ROC analysis for adiponectin showed that AUC was 0.958 at a cut-off point ≤0.74, the sensitivity and specificity were (90.0% and 95.0% respectively) for detection of Barrett esophagus in GERD patients denoting the protective effects of adiponectin. The protective effect of adiponectin observed in this study is consistent with the findings of several other epidemiological and molecular studies (Banks et al., 2000; Yamauchi et al., 2007).

In OE33 esophageal carcinoma cell lines, the role of adiponectin as an anti-proliferative factor was investigated. Adiponectin inhibits leptin-stimulated JAK2 activation as well as STAT3 transcriptional activity and enhances protein-tyrosine phosphatase 1B (PTP1B) protein expression and activity (Beales et al., 2014). Additional report has exhibited that increased adiponectin receptor expression together with higher leptin receptor protein levels have been measured in areas of intestinal metaplasia vs. that of the normal esophagus (Mokrowiecka et al., 2013).

We displayed remarkable associations between lower adiponectin level with the existence of large sliding hiatus hernia, long-segment Barrett in endoscopy as well as patients with high-grade dysplasia in histopathology. It was formerly stated that risk factors for the development of esophageal adenocarcinoma in patients with Barrett esophagus included large sliding hiatus hernia, long-segment Barrett and high-grade dysplasia (Wongsurawat et al., 2006). An experimental study of adiponectin and Barrett's

esophagus-associated esophageal adenocarcinoma found that adiponectin inhibits proliferation of leptin-induced EAC cells by activating 5'-AMP-activated kinase (AMPK) and serine/threonine phosphatases upon binding to and activating the adiponectin receptor-1. As adiponectin suppresses leptin-induced cell proliferation, high serum concentrations may protect against dysplasia or cancer development (Ogunwobi et al., 2008).

In the present study, univariate and multivariate regression analysis for parameters affecting obese patients with Barrett esophagus from obese patients with GERD showed that only lower adiponectin level is a risk factor and could be an independent predictor for Barrett's esophagus (BE).

STUDY LIMITATIONS

There were some limitations to our study. First, the number of participants in our study was limited. Second, follow up of studied patients is required to highlight the role of body weight control on adiponectin levels.

CONCLUSION

Our findings propose that obesity is a substantial risk for the development of GERD and Barrett's esophagus (BE), so adequate weight control is an important step for the prevention of Barrett's esophagus. Additionally, adiponectin plasma levels could be a reliable non-invasive biomarker for early prediction of Barrett's esophagus. Large population-based prospective studies are warranted to further appraise the effect of weight control on adiponectin level as well as its role in follow up after management of Barrett's esophagus.

AUTHORS' CONTRIBUTION

All authors contributed to the conception and designing of the work. NSE and ANZ selected the participants of the study. MAE did the laboratory studies and contributed to the interpretation. AME and NSE were the major contributors in the writing and revision of the manuscript. NSE and MAE corrected and edited the manuscript. All authors have read and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during this study are included in this published article.

ABBREVIATIONS

- AMPK: 5'-AMP-activated kinase
- BE: Barrett's esophagus
- BMI: body mass index (BMI
- EAC: Esophageal adenocarcinoma
- EGD: Esophgiogastroduodenoscopy
- GERG: gastro-esophageal reflux disease
- LES: lower esophageal sphincter
- PTP1B: protein-tyrosine phosphatase 1B

FUND

This work did not receive any fund.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Alexandre L, Long E, & Beales IL (2014). Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma. World Journal Gastrointestinal Pathophysiology, 15(4):534-49. doi: 10.4291/wjgp.v5.i4.534.

Al-Khalidy SH (2018). Association of Adiponectin with Gastroesophageal Reflux Disease. International Journal of Medical Research & Health Sciences7(8):141-145.

Almers LM, Graham JE, Havel PJ, & Corley DA (2015). Adiponectin May Modify the Risk of Barrett's Esophagus in Patients With Gastroesophageal Reflux Disease. Clinical Gastroenterology Hepatology, 13(13): 2256-64.e1-3. doi: 10.1016/j.cgh.2015.01.009.

Banks AS, Davis SM, Bates SH & Myers MG Jr (2000). Activation of downstream signals by the long form of the leptin receptor. Journal Biological Chemistry, 12;275(19):14563-72. doi: 10.1074/jbc.275.19.14563.

Beales ILP, Garcia-Morales C, Ogunwobi OO, & Mutungi G (2014). Adiponectin inhibits leptin-induced oncogenic signalling in oesophageal cancer cells by activation of PTP1B. Molecular and Cellular Endocrinology, 25: 382(1):150-158. doi: 10.1016/j.mce.2013.08.013.

Boeckxstaens G, El-Serag HB, Smout AJ, & Kahrilas PJ (2014). Symptomatic reflux disease: the present, the past and the future. Gut, 63(7): 1185-93. doi: 10.1136/gutjnl-2013-306393.

Calabro P & Yeh ET (2008). Intra-abdominal adiposity, inflammation, and cardiovascular risk: new insight into global cardiometabolic risk. Current Hypertension Reports, 10(1): 32-8. doi: 10.1007/s11906-008-0008-z.

Carrossini N, Meireles Da Costa N, Andrade-Barreto E, Sousa VPL, Nicolau-Neto P, Souza-Santos PT, Mansur GR, Wernersbach, Bozza PT, Viola JPB& Luis Felipe Ribeiro Pinto (2021). Lipid droplet biogenesis and COX-2 pathway activation are triggered by Barrett's esophagus and adenocarcinoma, but not esophageal squamous cell carcinoma risk factors. Scientific Reports, 11: 981. https://doi.org/10.1038/s41598-020-80035-4

Choe JW, Kim YC, Joo MK, Kim HJ, Lee BJ, Kim JH, Yeon JE, Park JJ, Kim JS, Byun KS, & Bak YT (2016). Application of the Prague C and M criteria for endoscopic description of columnar-lined esophagus in South Korea. World Journal of Gastrointestinal Endoscopy, 25(8):357-61. doi: 10.4253/wjge.v8.i8.357.

Dent J, El-Serag HB, Wallander MA, & Johansson S (2005). Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut, 54(5): 710-7. doi: 10.1136/gut.2004.051821.

Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, & Vaughan TL (2007). Central adiposity and risk of Barrett's esophagus. Gastroenterology, 133(2): 403-11. doi: 10.1053/j.gastro.2007.05.026.

El-Serag HB, Hashmi A, Garcia J, Richardson P, Alsarraj A, Fitzgerald S, Vela M, Shaib Y, Abraham NS, Velez M, Cole R, Rodriguez MB, Anand B, Graham DY, & Kramer JR (2014). Visceral abdominal obesity measured by CT scan is associated with an increased risk of Barrett's oesophagus: a case-control study. Gut, 63(2):220-9. doi: 10.1136/gutjnl-2012-304189.

El-Serag HB, Kvapil P, Hacken-Bitar J, & Kramer JR (2005). Abdominal obesity and the risk of Barrett's esophagus. The American Journal of Gastroenterology, 100(10):2151-6. doi: 10.1111/j.1572-0241.2005.00251.x.

Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, Blot WJ, Gail MH, & Fraumeni JF Jr (2003). Population attributable risks of esophageal and gastric cancers. Journal of the National Cancer Institute, 17; 95(18):1404-13. doi: 10.1093/jnci/djg047.

Fadel HH, Hefny NE, Yousef AI, Sadek NA, Attea E, & El-Sewedy T (2020). The association of adiponectin polymorphism (rs2241766) with susceptibility and prognosis of Egyptian patients with hematological malignancies: A case-control study. International Journal of Cancer and Biomedical Research 4(1): 57-68. Doi: 10.21608/jcbr.2020.25954.1014

Fasshauer M, Klein J, Neumann S, Eszlinger M, & Paschke R (2002). Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochemical and Biophysical Research Communications, 25;290(3):1084-9. doi: 10.1006/bbrc.2001.6307.

Garcia JM, Splenser AE, Kramer J, Alsarraj A, Fitzgerald S, Ramsey D, & El-Serag HB (2014). Circulating inflammatory cytokines and adipokines are associated with increased risk of Barrett's esophagus: a case-control study. Clinical Gastroenterology Hepatology, 12(2): 229-238.e3. doi: 10.1016/j.cgh.2013.07.038.

GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, & Murray CJL. (2017). Health Effects

of Overweight and Obesity in 195 Countries over 25 Years. New England Journal of Medicine, 6(1): 13-27. doi: 10.1056/NEJMoa1614362.

Greer KB, Falk GW, Bednarchik B, Li L, Chak A (2015). Associations of Serum Adiponectin and Leptin With Barrett's Esophagus. Clinical Gastroenterology Hepatology, 13(13): 2265-72. doi: 10.1016/j.cgh.2015.02.037.

Kelesidis I, Kelesidis T, & Mantzoros CS (2006). Adiponectin and cancer: a systematic review. British Journal of Cancer, 8(9): 1221-5. doi: 10.1038/sj.bjc.6603051.

Konturek PC, Burnat G, Rau T, Hahn EG, & Konturek S (2008). Effect of adiponectin and ghrelin on apoptosis of Barrett adenocarcinoma cell line. Digestive diseases and sciences, 53(3): 597-605. doi: 10.1007/s10620-007-9922-1.

Labenz J (2009). Extraösophageale Manifestationen der Refluxkrankheit: eine kritische Analyse [Extraesophageal manifestations of gastroesophageal reflux disease: a critical analysis]. Dtsch Med Wochenschr,134(37): 1812-6. German. doi: 10.1055/s-0029-1237516.

Makimura H, Mizuno TM, Bergen H, & Mobbs CV (2002). Adiponectin is stimulated by adrenalectomy in ob/ob mice and is highly correlated with resistin mRNA. American journal of physiology. Endocrinology and Metabolism, 283(6): E1266-71. doi: 10.1152/ajpendo.00227.2002.

Moayyedi P (2008). Barrett's esophagus and obesity: the missing part of the puzzle. American Journal of Gastroenterology,103(2): 301-3. doi: 10.1111/j.1572-0241.2007.01618.x.

Mokrowiecka A, Daniel P, Jasinska A, Pietruczuk M, Pawlowski M, Szczesniak P, Orszulak-Michalak D, & Malecka-Panas E (2012). Serum adiponectin, resistin, leptin concentration and central adiposity parameters in Barrett's esophagus patients with and without intestinal metaplasia in comparison to healthy controls and patients with GERD. Hepatogastroenterology, 59(120): 2395-9. doi: 10.5754/hge12587.

Mokrowiecka A, Sokolowska M, Luczak E, Dudojc M, Wieczfinska J, Kacprzak D, Wierzchniewska-Lawska A, Pawliczak R, & Malecka-Panas E (2013). Adiponectin and leptin receptors expression in Barrett's esophagus and normal squamous epithelium in relation to central obesity status. Journal of physiology and pharmacology: an official journal of the Polish Physiological Society, 64(2): 193-9.

Nam SY, Choi IJ, Ryu KH, Park BJ, Kim YW, Kim HB, & Kim JS (2015). The effect of abdominal visceral fat, circulating inflammatory cytokines, and leptin levels on reflux esophagitis. Journal of neurogastroenterology and motility, 30;21(2): 247-54. doi: 10.5056/jnm14114.

Ogunwobi OO & Beales IL (2008). Globular adiponectin, acting via adiponectin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. Molecular and cellular endocrinology, 26(1-2): 43-50. doi: 10.1016/j.mce.2008.01.023..

Ou JL, Tu CC, Hsu PI, Pan MH, Lee CC, Tsay FW, Wang HM, Cheng LC, Lai KH, & Yu HC (2012). Prevalence and risk factors of erosive esophagitis in Taiwan. Journal of the Chinese Medical Association: JCMA, 75(2): 60-4. doi: 10.1016/j.jcma.2011.12.008.

Rafat MN, Younus HA, El-Shorpagy MS, Hemida MH, El Shahawy MS, & El Sayed Atiia AAEA (2018). Adiponectin level changes among Egyptians with gastroesophageal reflux disease. JGH open: an open access journal of gastroenterology and hepatology, 28(1): 21-27. doi: 10.1002/jgh3.12038.

Reaven GM (1992). Syndrome X. Blood pressure. Supplement, 4:13-6. PMID: 1345329.

Reaven G (2002). Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. Circulation, 16(3): 286-8. doi: 10.1161/01.cir.0000019884.36724.d9.

Roman S and Pandolfino JE (2010). Environmental - lifestyle related factors. Best practice & research. Clinical Gastroenterology, 24(6): 847-59. doi: 10.1016/j.bpg.2010.09.010.

Rubenstein JH, Dahlkemper A, Kao JY, Zhang M, Morgenstern H, McMahon L, & Inadomi JM (2008). A pilot study of the association of low plasma adiponectin and Barrett's esophagus. The American journal of gastroenterology,103(6): 1358-64. doi: 10.1111/j.1572-0241.2008.01823.x.

Rubenstein JH, Kao JY, Madanick RD, Zhang M, Wang M, Spacek MB, Donovan JL, Bright SD, & Shaheen NJ (2009). Association of adiponectin multimers with Barrett's oesophagus. Gut, 58(12): 1583-9. doi: 10.1136/gut.2008.171553.

Russo A, Franceschi S, La Vecchia C, Dal Maso L, Montella M, Conti E, Giacosa A, Falcini F, & Negri E (1998). Body size and colorectal-cancer risk. International Journal of Cancer, 5(2): 161-5. doi: 10.1002/(sici)1097-0215(19981005)78:2<161:aid-ijc7>3.0.co;2-x.

Ryan AM, Duong M, Healy L, Ryan SA, Parekh N, Reynolds JV, & Power DG (2011). Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and

new targets. Cancer Epidemiology, 35(4): 309-19. doi: 10.1016/j.canep.2011.03.001.

Sharma P, Wani S, Romero Y, Johnson D, & Hamilton F (2008). Racial and geographic issues in gastroesophageal reflux disease. The American Journal Of Gastroenterology,103(11): 2669-80. doi: 10.1111/j.1572-0241.2008.02089.x.

Stein DJ, El-Serag HB, Kuczynski J, Kramer JR, & Sampliner RE (2005). The association of body mass index with Barrett's oesophagus. Alimentary pharmacology & therapeutics,22(10): 1005-10. doi: 10.1111/j.1365-2036.2005.02674.x.

Thompson OM, Beresford SA, Kirk EA, Bronner MP, & Vaughan TL (2010). Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. Obesity (Silver Spring). 18(11): 2204-11. doi: 10.1038/oby.2009.508.

Vaezi MF & Richter JE (1996). Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. Gastroenterology, 111(5): 1192-9. doi: 10.1053/gast.1996.v111.pm8898632.

Viengchareun S, Zennaro MC, Pascual-Le Tallec L, & Lombes M (2002). Brown adipocytes are novel sites of expression and regulation of adiponectin and resistin. FEBS letters, 532(3): 345-50. doi: 10.1016/s0014-5793(02)03697-9.

Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, & Tataranni PA (2001). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. The Journal of clinical endocrinology and metabolism, 86(5): 1930-5. doi: 10.1210/jcem.86.5.7463.

Wongsurawat VJ, Finley JC, Galipeau PC, Sanchez CA, Maley CC, Li X, Blount PL, Odze RD, Rabinovitch PS, & Reid BJ (2006). Genetic mechanisms of TP53 loss of heterozygosity in Barrett's esophagus: implications for biomarker validation. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 15(3): 509-16. doi: 10.1158/1055-9965.

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, & Kadowaki T (2007). Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nature medicine, 13(3): 332-9. doi: 10.1038/nm1557.

Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS; INTERHEART Study Investigators (2005). Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet, 5;366(9497): 1640-9. doi: 10.1016/S0140-6736(05)67663-5.