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Association of Adiponectin with Gastroesophageal Reflux Disease

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ABSTRACT

Background: *Gastroesophageal reflux disease (GERD) has become the most frequently seen gastrointestinal disorder in outpatient clinics. The esophageal mucosal epithelium will be affected by gastric acidity due to the altered gastroesophageal junction.* ***Aim of the study:*** *To examine the association between circulating levels of adiponectin and GERD among patients undergoing upper endoscopy.* ***Type of the study:*** *A case-control study.* ***Patients and methods:*** *A planned study by Al-Kindy College of Medicine, done from January 2017 to May 2018. Data were collected from 40 GERD patients and 30 healthy control individuals and endoscopy were done for them. Their weight, height, waist circumference, body mass index was calculated. Lipid profile and adiponectin were done for them.* ***Results:*** *The results showed that there was a strong negative correlation between adiponectin and age, height, weight, BMI, waist circumference, waist to hip ratio, cholesterol, triglyceride, LDL. There is only a positive correlation between adiponectin and HDL and LDL/HDL (+0.214 and +0.014 respectively).* ***Conclusions:*** *This present study highlights that derangement of circulating adiponectin gut hormones is involved in the pathogenesis of GERD and may predispose to Barrett's esophagus.*

Keywords: Adiponectin, GERD, Lipid

INTRODUCTION

Gastroesophageal reflux disease (GORD) has increased remarkably over the past few decades and it is well known as a risk factor for Barrett's oesophagus and oesophageal adenocarcinoma [1]. It increases the risk by 30-40-fold [2]. Many mechanisms contribute to the pathogenesis of GERD and affect the function of the gastroesophageal junction like obesity and increased abdominal pressure [3]. Another circulating metabolic factor that is related to obesity is adiponectin [4]. Adiponectin is a deposed specific protein or peptide produced by adipose tissue and visceral Adipocyte, and its level is inversely correlated with obesity and lower in males than females [5]. It had many functions like regulation of inflammation and suppress carcinogenesis [6,7]. It induces a high level of TNF alpha and weight loss in animals through adiponectin promoter activator NP-1 [8]. It also attenuates oxygen-glucose deprivation-induced mitochondrial oxidative injury and apoptosis via the JAK2/STAT3 pathway [9]. It mediates its action through its binding to specific receptors which are AdipoR1 and AdipoR2 present in the mucosa of the oesophagus [10]. The association between adiponectin and GERD or Barrett's oesophagus are contradictory. One study found that low plasma levels of adiponectin in patients with dyspepsia and heartburn are associated with an increased risk of Barrett's oesophagus among patients undergoing upper endoscopy for confirming the diagnosis [11]. On the other hand, another pilot study did not detect such a relationship [12].

Thus, it was hypothesized that a decrease in the adiponectin level is a risk factor for GERD. So this a case-control study performed to examine the association between circulating levels of adiponectin and GERD among patients undergoing upper endoscopy.

PATIENTS AND METHODS

The study is a case-controlled planned study by Al-Kindy College of Medicine, done from January 2017 to May 2018. The consent of medicinal morals board was obtained from participants in this study. The revision was accepted by the Al-Kindy College of Medicine and Al-Kindy Teaching Hospital. The knowledgeable permission was obtained

from patients. The Scientific and Ethical Committee of Al-Kindy Medical College and Al-Kindy Teaching Hospital had approved and registered the study. Written informed consents were obtained from the patients and control normal blood donors.

Inclusion Criteria

Patients complaining from dyspepsia, upper abdominal discomfort, acid regurgitation of at least one per month for the past 6 months, heartburn more than 3 days per week according to Montreal definition and classification of gastroesophageal reflux disease were included in the study [13].

Exclusion Criteria

Patients who had a history of gastric surgery, peptic ulcer, gastric cancer, previous *H. pylori* eradication, esophageal varices and patients who were on medications like antacids, H2 blockers, proton pump inhibitors and non-steroidal anti-inflammatory drugs were excluded from the study.

Data were collected from 40 GERD patients and 30 healthy control individuals including demographic information like age, sex and residential status by questionnaire.

Endoscopy

All patients underwent upper gastrointestinal endoscopic examinations using gastroscopy: GIF-H260; Olympus, Tokyo, Japan and Display screen; Olympus OEV-261H liquid crystal display monitor; Olympus, Tokyo, Japan. An endoscopic examination was performed by well-trained gastroenterologists with at least 5 years of endoscopy experience. The gastroesophageal junction was defined as the squamocolumnar junction and the proximal margin of gastric folds. The presence or absence of GERD was determined by endoscopist according to their criteria [14].

Anthropometric Measurements

Weight, height, waist circumference, body mass index was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured in centimeters (cm) at the end of normal expiration halfway between the lowest rib and the iliac crest with the examiner standing at the side to ensure that the measuring tape is horizontal across the back and the front of the participant [15].

Blood Collection and Analysis

Blood was obtained from the 2 groups, 5 ml venous blood was aspirated from a suitable vein. Blood samples were divided into 2 parts, one for lipid profile and the remaining for the rest analysis of other parameters.

Each serum sample was analyzed for lipid profile (cholesterol, triglyceride, HDLP, LDLP (Human-Germany), adiponectin (Shanghai Biologic Technology-China), C-reactive protein (Human-Germany) and *H pylori* (Eco test-China).

Statistical Analysis

Statistical analysis was done using MiniTab version 3.0 software. Data analysis was done using a chi-square test for frequencies, while t-test for means and standard Error Mean. The correlation coefficient was used to find the correlation between different parameters by Pearson correlation. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The total number of study groups was 60 individuals, 40 of them were GERD and the rest were controlled healthy subjects. The patient's group age was 42.25 ± 2.41 which is not significant with control group 38.27 ± 3.78 (p=0.387). Males 22 (55%) were more than females 18 (45%) in patients group which is a significant difference from the control group (p=0.028). BMI is significantly higher in GERD patients (p=0.011) in comparison with control. In this study, adiponectin and lipid profile except TG were significantly higher in the patient group (Table 1). Most of GERD patients were positive for C-reactive protein and *H pylori* (p=0.000).

Table 1 Demographic difference of various parameters between patients with gastroesophageal reflux disease (GERD) and control group

Parameters	GERD patients N=40	Control Group N=20	p-value
	X ± SEM	X ± SEM	
Age (year)	42.25 ± 2.41	38.27 ± 3.78	0.387
Range	(25-62)	(25-68)	
Male %	22 (55%)	14 (70%)	0.028
Female %	18 (45%)	06 (30%)	
Height (cm)	165.55 ± 0.0170	172.30 ± 0.0265	0.048
Weight (Kg)	76.05 ± 2.92	82.23 ± 5.51	0.338
BMI Kg/m^2	31.78 ± 1.04	27.41 ± 1.13	0.011
Waist circumference (cm)	120.10 ± 3.02	103.90 ± 5.24	0.005
Waist to Hip Ratio	1.036 ± 2.30	1.114 ± 3.43	0.984
Adiponectin Mg/ml	15.240 ± 1.462	9.119 ± 2.315	0.023
Cholesterol Mg/ml	287.0 ± 26.3	104.7 ± 52.1	0
Triglyceride Mg/ml	140.0 ± 25.3	137.0 ± 75.8	0.962
HDL Mg/ml	35.80 ± 3.40	50.42 ± 4.25	0.012
LDL Mg/ml	212.1 ± 25.9	155.1 ± 39.3	0.219
LDL/H|DL	4.5 ± 0.0614	2.688 ± 0.283	0
C-reactive protein +	20 (50%)	1 (2.5%)	0
H. pylori +	26 (65%)	1 (2.5%)	0

The results showed that there was a strong negative correlation between adiponectin and age, height, weight, BMI, waist circumference, waist to hip ratio, cholesterol, Triglyceride, LDL. There is only a positive correlation between adiponectin and HDL and LDL/HDL (+0.214 and +0.014 respectively) as shown in Table 2.

Table 2 Pearson correlation analysis of adiponectin with different parameters in GERD patients

Parameters	Patients with GERD N=40 r	p-value
Age (year)	-0.284	0.225
Height (cm)	-0.311	0.182
Weight (Kg)	-0.325	0.162
BMI Kg/m^2	-0.145	0.541
Waist (cm)	-0.396	0.084
Hip Waist Ratio	-0.079	0.742
Cholesterol Mg/dl	-0.215	0.362
Triglyceride Mg/dl	-0.118	0.621
HDL Mg/dl	0.214	0.365
LDL Mg/dl	-0.009	0.969
LDL/HDL	0.014	0.953

DISCUSSION

The pathogenesis of GERD is complex and multifactorial. Obesity and increased body mass index are one of the predisposing factors. In this study, there is a significant increase of BMI, waist circumference and waist to hip ratio in GERD patients in comparison with a control group which is in agreement with other studies [16,17]. There are many explanations on the role of obesity in GERD development, one of the adiponectin peptides is secreted from adipose tissue and play an important role in motility of gastric intestinal tract and derangement of circulating of this peptide might participate in mucosal inflammation and symptoms in patients with GERD [18]. The correlation between the low circulating adiponectin and central obesity is well established [19]. It had a central effect on monocytes as an anti-inflammatory factor and neurosensorial protective effect, so its deficiency has been associated with several

inflammatory gastrointestinal diseases [20]. This study showed a significant increase of adiponectin when compared with control group (p=0.023) with negative correlation. This is in agreement with other studies [21,22]. These higher adiponectin concentrations may either be responsible for the aberrant healing of esophageal mucosa that leads to metaplasia and Barrett's esophagus or is a marker for other factors [23]. Other study showed that visceral fat may increase the risk of GERD by increasing the levels of inflammatory cytokines and adiponectin [24]. Thus, a high level of adiponectin in GERD patients may be a protective against Barrett's esophagus [25]. Regarding lipid profile, this study showed a significant increase in lipid profile when compared with control except for triglyceride and there was a negative correlation with them which is in agreement with another study. It regulates free fatty acid oxidation in mouse muscle and liver that regulates the production of proteins associated with triglyceride metabolism, acyl CoA oxidase, activated protein kinase, and peroxisome proliferator-activated receptor γ (PPARγ) [26].

Despite methodological limitations and the small sample size, this study showed that the role of abdominal obesity on the risk of GERD mediated by adiponectin rather than a mechanical effect of obesity-promoting GERD. Thus, decreased anti-inflammatory cytokines, such as adiponectin, may be associated with the development of GERD-related reflux symptoms, erosive esophagitis, and Barrett's esophagus.

CONCLUSION

This present study highlights that derangement of circulating adiponectin gut hormones is involved in the pathogenesis of GERD and may predispose to Barrett's esophagus.

RECOMMENDATIONS

Further prospective studies involve a larger case number, and outcome measure and follow-up the patients after therapeutic treatment of GERD patients.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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