Adipnectin level in gastroesophageal reflux disease

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Abstract: Objectives: to evaluate serum adiponectin in gastro-oesophageal reflux patients and its correlation with obesity. **Background:** Gastroesophageal reflux disease (GERD) is a common disorder, it develops when the gastric content pass to the esophagus which prompt disability of personal satisfaction. Several factors may predispose to reflux including smoking, alcohol, drugs and large night meals. Obesity is known to be an independent risk factor for GERD through Decrease tone of lower esophageal sphincter. Abdominal obesity not only mechanically disrupts the integrity of the gastro-esophageal junction barrier which leads to increased esophageal reflux but also has a metabolically mediated effect through secretion of adipocytokines**. Methods:** A case-control study was performed between October 2014 to January 2016 in Internal Medicine department; Menofia University Hospital. One hundred subjects were included in this study and classified into 3 groups: Group (I) included twenty healthy individuals with average BMI serve as a control group. Group (II) included forty obese patients with GERD symptoms confirmed by upper endoscopy with BMI >24kg. Group (III) included forty non-obese patients with GERD symptoms confirmed by upper endoscopy. Clinical factor and laboratory investigation were compared between subjects with and without GERD as well as serum adiponectin measurement by ELIZA for all groups. **Results:** Serum adiponectin levels were significantly lower in obese patients with GERD and in non-obese patients with GERD compared to those in healthy control (P<0.001). Low level of circulating adiponectin was associated with Barrett's esophagus. Receiver operating characteristic curve showed that the best cutoff value for serum adiponectin was 7.67 (µg/ml) with a sensitivity of 95% and specificity of 94%. **Conclusions:** Low serum adiponectin levels may be associated with an increased risk for GERD in obese patients.
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Introduction:

Gastro-esophageal reflux disease (GERD) is a common disorder known as the passage of gastric contents into the esophagus at least once a week due to the failure of antireflux mechanisms which leads to symptoms such as heartburn or acid regurgitation **(1).** GERD may be classified as erosive esophagitis or non-erosive esophagitis. Patients with non-erosive esophagitis have no mucosal breaks in the esophagus but have reflux symptoms such as heartburn, bleaching, waterbrash, and odynophagia in contrast to patients with erosive esophagitis have mucosal breaks seen by endoscopy as well as typical reflux symptoms **(2).** Regurgitation or aspiration of gastric juice in GERD may cause a chronic cough, laryngitis, recurrent pneumonitis or idiopathic pulmonary fibrosis and nocturnal choking or asthma **(3).** Less common complications include hemorrhage, stricture, Barrett's esophagus and adenocarcinoma **(4).** The intra-abdominal esophagus acts as a valve providing an additional anti-reflux barrier. Transient LES relaxation (t-LESr) and hiatus hernia predispose to the occurrence of GERD **(5).** Obesity is an independent risk factor for GERD and odds ratio (OR) for overweight is approximately (1.5) fold and for obese individuals is (2-3) fold. Visceral fat or abdominal obesity is associated with GERD through elevates intra-abdominal pressure by increasing acid reflux to the esophagus which leads to the occurrence of GERD **(6).** Visceral fat is an important endocrine organ that secretes different bioactive substances such as adipocytokines. So, obesity may affect the pathogenesis of GERD by adipocytokines as well as acid reflux **(7).** Adiponectin is an adipocytokine that was isolated from the human adipose tissue. It is ranged from (5–30 µg/ml) in the human blood and serum levels are inversely correlated with BMI **(8).** Adiponectin has anti-inflammatory, Anti-steatotic, anti-diabetic and anti-malignant effects. Epidemiologic studies including our study have indicated that lower serum adiponectin levels are associated with various inflammatory diseases of the digestive system. Based on these experimental and epidemiologic results, we hypothesize that adiponectin is involved in the pathogenesis of GERD **(9, 10).**

The aim of this study was to evaluate serum adiponectin in gastro-oesophageal reflux patients and its correlation with obesity.

2. Subjects and Methods:

Subjects:

This was a case-control observational study from October 2014 to January 2016. Subjects were selected from Internal Medicine department; an outpatient clinic in Menofia University Hospital with age ranged from 20-70 years of 31 males and 69 females. Informed consent from all patients and controls were obtained in accordance with the local ethical committee.

Sample size justification:

MedCalc® version 12.3.0.0 program was used for calculations of sample size, statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%**,** According to a previous study **(17),** showed that the serum adiponectin of erosive esophagitis [Present 8.17 ± 0.365 versus Absent 10.1 ± 0.120] and mean differance [1.93] with p-value <0.001 highly significant, So it can be relied upon in this study, based on this assumption, sample size was calculated according to these values produced a minimal samples size of 95 cases were enough to find such a difference. Assuming a drop-out ratio of 5%, the sample size was 100 women in each group.

Study groups:-

One hundred subjects were included in this study and classified into 3 groups: Group (I): included twenty healthy individuals with average BMI don't complain of any G.I.T symptoms serve as control group. Group (II): included forty obese patients with GERD symptoms confirmed by upper endoscopy with BMI > 24kg. Group (III): included forty non-obese patients with GERD symptoms with average BMI and confirmed by upper endoscopy with the grading of GERD according to loss Angelos classifications.

Study design:

All subjects were subjected to the following: Full history taking and physical examinations.

Laboratory investigation:

CBC, FBG, serum triglyceride, serum cholesterol, ALT, AST and serum creatinine was investigated.

Measurement of serum adiponectin (human total adiponectin / Immunoassay, R&D system 2015):

Blood tests have been acquired in the morning following 12 hours fasting from patients of all analyzed groups and controls before upper gastrointestinal endoscopy. Blood serum was obtained after 15 minutes clotting and centrifugation at 2000 rpm for 10 minutes. Serum was removed and stored frozen at –20°C. Adiponectin concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, USA).

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) Statistics version 16 (IBM© Corp., Armonk, NY, USA). Using tests: Chi-square-test **(X2):** for comparison of qualitative data. Analysis of Variance (ANOVA) was done for comparison of quantitative data between groups. Odds ratio analysis was conducted to compare the probability that cases had been exposed to certain risk factors increase the incidence of GERD. Logistic regression analysis was carried out to assess the direction, strength significant and value of the factor in relation to the occurrence of GERD. Differences were considered statistically significant when $P < 0.05$. Receiver Operating Characteristic (ROC) curves were used to interpret sensitivity and specificity levels and to determine related cut scores.

3. Results:

Characteristics of the included subjects are Age between 20- 70 years, no previous gastroesophageal surgery, no previous gastro-esophageal cancer, no history of major stroke or mental conditions, the study population included more women than men. The present study included 100 subjects 31 males and 69 females classified into 3 groups: Group (I): included twenty normal individuals (6 men and 14 female; mean age 46.8±13). Group (II): included forty obese patients with GERD symptoms (12 men and 28 female; mean age 48.7± 12). Group (III): included forty non-obese patients with GERD symptoms (13 men and 27 female; mean age 43.3±10.7). All patients suffered from daily reflux symptoms for at least one year **(Table 1).** Endoscopic finding of studied groups was illustrated Erosive esophagitis in 38 cases (95%) of the group (II) and 27 cases (67.5%) of the group (III). In the present study, most erosive esophagitis patients were of moderate (42.5%) to severe (30%) in the group (II) and most erosive esophagitis patients were of mild (65%) of the group (III) with no erosions in (32.5%) as shown in **(Table 2).** Laboratory investigation of studied groups showing significance difference between studied groups regarding FBG, S. triglyceride, S. cholesterol and adiponectin as shown in **(Table 3).** The percentage of serum adiponectin was (100%, 100%, 94.4%, 83.3%, 20%) with (Barrett's esophagus, Severe erosion (C), Moderate erosion (B), Mild erosion (A), No erosion) respectively indicate low level of adiponectin was associated with high prevalence of erosive esophagitis and Barrett's esophagus as shown in **(Table 4).** The effect of special habits and other factors on gastro-esophageal reflux disease among the control group (I) and cases group (II+III) was found that subjects who exposed to obesity were at risk three and half times more than those not exposed. Subjects who smoking was at risk two times more than those non-smokers. It was found that the risk for NSAID in taking was doubled for those not taking NSAID as shown in **(Table 5).**

Receiver operating characteristic curve showed that the best cutoff value for serum adiponectin was 7.67 (µg/ml) with a sensitivity of (95%) and specificity of (94%). The area under the curve was (0.98) closer to 1 indicate the screening measure reliably as shown in **(Table 6, Fig.2).** Serum adiponectin levels were significantly lower among obese subjects with GERD than among non-obese with GERD and those without GERD **(Fig. 1).**

Table (1): - Demographic characteristics of patients in the studied groups:-

Studied group Items	Group (I) NO.=20		Group (II) NO.=40		Group (III) NO.=40		Test of Significance	*P.* value
	NO	%	NO	%	NO	%		
Age group 20-40 40-60 >60	 8 9 3	 40 45 15	 12 20 8	 30 50 20	 21 14 5	 52.5 35 12.5	$\chi^2 = 5.3$	0.5
Age (yr) (mean ± SD)	46.8±13		48.7±12		43.3±10.7		ANOVA F=2.1	0.1
Gender Male Female	 6 14	 30 70	 12 28	 30 70	 13 27	 32.5 67.5	$\chi^2 = 0.07$	0.9

Table (2): - Endoscopic finding of studied groups:

Studied group Items	Control (I) N.=20		Group (II) N.=40		Group (III) N.=40		Test of Significance	*P.* value
	NO	%	NO	%	NO	%		
Endoscopic finding Not done No erosive finding Mild erosion (A) Moderate erosion (B) Sever erosion (C) Barrett's esophagus	 20 — — — — —	 100 — — — — —	 0 2 4 17 12 5	 0 5 10 42.5 30 12.5	 0 13 26 1 0 0	 0 32.5 65 2.5 0 0	$\chi^2 = 1.6$	<0.001

Table (3): - Comparison between studied groups regarding lab investigations:-

Studied group Items	Group (I) N.=20		Group (II) N.=40		Group (III) N.=40		Test of Significance	*P.* value
	NO	%	NO	%	NO	%		
FBG group (mg\dl) ≤110 110>	 19 1	 95 5	 0 40	 0 100	 10 30	 25 75	$\chi^2 = 58.9$	<0.001
TRI group (mg\dl) 150≥ 150>	 20 0	 100 0	 4 36	 10 90	 27 13	 67.5 32.5	$\chi^2 = 50.5$	<0.001
T.CHO group (mg\dl) ≤240 240>	 20 0	 100 0	 1 39	 2.5 97.5	 16 24	 40 60	$\chi^2 = 54.6$	<0.001
S. adiponectin group (µg/ml) <5 µg (5-30 µg)	 0 20	 0 100	 39 1	 97.5 2.5	 23 17	 57.5 42.5	$\chi^2 = 54.4$	<0.001

Table (4): -Relation between serum adiponectin and endoscopic finding:-

	S. adiponectin <5 ng		S. adiponectin (5-30 ng)		Significance test	P. value
Endoscopic finding	No	%	No	%		
No erosion	3	20	12	80	**x^2=36.9**	**<0.001**
Mild erosion (A)	25	83.3	5	16.7		
Moderate erosion (B)	17	94.4	1	5.6		
Severe erosion (C)	12	100	0	0		
Barrett's esophagus	5	100	0	0		

Table (5): Multivariable logistic regression analysis for the relation between adiponectin and GERD as adjusted for confounding factors:-

Studied group / predictor	*Group (I) N.=20		Group (II+III) N.=80		Test of significance	Odds Ratio	95% Confidence Interval (LL-UL)
	NO	%	NO	%			
Sex							
Male	**6**	**30**	**25**	**31.2**	χ^2 **=0.1**	**2.1**	**(1.6 - 2.8)**
female	**14**	**70**	**55**	**68.8**	***P.* Value=0.9**		
Obesity							
Non-obese	**20**	**100**	**49**	**61.2**	χ^2 **=11.2**	**3.5**	**(2.2- 5.3)**
Obese	**0**	**0**	**31**	**38.8**	***P.* Value<0.001**		
Smoking							
Yes	**7**	**35**	**66**	**82.5**	χ^2 **=18.3**	**2.1**	**(1.5- 3)**
No	**13**	**65**	**14**	**17.5**	***P.* Value<0.001**		
Coffee drinking							
Yes	**6**	**30**	**61**	**76.2**	χ^2 **=15.5**		
No	**14**	**70**	**19**	**23.8**	***P.* Value<0.001**	**2**	**(1.5- 2.9)**
NSAID							
Yes	**6**	**30**	**48**	**54**	χ^2 **=5.8**	**2**	**(1.5- 2.9)**
No	**14**	**70**	**32**	**46**	***P.* Value<0.001**		
H. hernia							
Yes	**0**	**0**	**34**	**42.5**	χ^2 **=12.8**	**1.9**	**(1.4 – 2.5)**
No	**20**	**100**	**46**	**57.5**	***P.* Value<0.001**		
TRI. groups							
≤150	**19**	**95**	**31**	**38.8**	χ^2 **=24**	**3.3**	**(2.2 – 4.9)**
>150	**1**	**5**	**49**	**61.2**	***P.* Value<0.001**		
T.CHO groups							
≤240	**18**	**90**	**17**	**21.2**	χ^2 **=42.5**	**3.2**	**(2.2 – 4.6)**
>240	**2**	**10**	**63**	**78.8**	***P.* Value<0.001**		
FBG							
≤110	**19**	**95**	**10**	**12.5**	χ^2 **=52.8**	**3**	**(2.1 – 4.3)**
>110	**1**	**5**	**70**	**87.5**	***P.* Value<0.001**		

*Reference group is the control group (I)

Group (I):- control group, Group (II +III):- obese and non-obese.

Table (6): - Receiver operating characteristic of adiponectin serum related to GERD:

*AUC	Sensitivity	Specificity	Cut off point
0.98	**95%**	**94%**	**7.67**

*AUC: Area under the curve.

4. Discussion:

Obesity especially visceral obesity is an important independent risk factor for the development of GERD, Barrett's esophagus and adenocarcinoma **(11).** Visceral fat has been discharging a few proinflammatory cytokines e.g TNF-α, IL 1and IL 6 which can diminish esophageal muscle constriction by restraining acetylcholine discharge **(12, 13).**

In the present study serum adiponectin was lower in group (II) and group (III) than in control group (I), the same finding was reported by Abdel Kader A.N et al **(15)** and Ayumu H **(16)** in addition to high association of erosive esophagitis with lowering level of serum adiponectin as reported by Motohiko et al **(17).**

Also in our study, we found an inverse relation between plasma adiponectin and serum triglyceride levels as well as a fasting plasma glucose concentration in agreement with Hotta K. et al **(18)** and Weyer C et al **(19).**

Iwasaki E et al **(20)** announced that diminished level of adiponectin appeared in a patient with extreme GERD assessed by video esophagography and this level associated contrarily with BMI, HOMA-IR and triglyceride level.

The prevalence of erosive esophagitis and reflux symptoms in this study was 81.2 and 92.8% respectively, which was near to the resulted of Tai C.M et al **(21).** In addition to the high prevalence of erosive esophagitis and reflux symptoms, we also demonstrated that the presence of reflux symptoms was associated with erosive esophagitis in this study.

In the present study erosive esophagitis (EE) was associated with significantly lower adiponectin levels than non-erosive esophagitis (NE), which is consistent with a recent study by Motohiko K et al **(17)** who analyzed 2405 subjects underwent a health check-up and found that men with low serum adiponectin levels were more powerless to EE. In any case, they didn't research the relationship of adiponectin with GERD side effect.

Our study has further shown that adiponectin levels were also inversely associated with severity of symptoms which was consistent with a Japanese study showing an inverse relationship between adiponectin levels and GERD symptoms in obese patients **(20).**

Negative correlation between plasma adiponectin levels and body mass index or body fat was further supported by studies of Weyer et al **(19)** performed on Caucasian and Pima Indian populations**.**

Hirata et al. **(22)** additionally demonstrated that concurrence of metabolic disorder and low levels of serum adiponectin was related with a higher commonness and higher recurrence of GERD indications in subjects with type 2 diabetes mellitus.

A current review from Nam S.Y. et al **(23)** additionally exhibited that instinctive fat may build the danger of reflux esophagitis by expanding the levels of fiery cytokines. The hidden system for the aggravation and side effect discernment might be in part clarified by the calming and neurosensorial defensive impact of adiponectin **(24,25).**

Moreover, significantly lower plasma adiponectin levels were noted in BE patients in the present study which are similar results to those of a case-control study conducted by Rubenstein et al **(26)** Despite methodologic limitations and the small sample size (5 subjects in this group)**.**

BE was associated with low levels of anti-inflammatory cytokines and statistically significant lower adiponectin levels. Serum hypoadiponectinemia in BE was shown in previous studies **(27, 28).**

Conclusion:

Adiponectin plasma level is inversely related to obesity with an increased risk of GERD. This suggests that visceral fat accumulation is associated with impaired secretion of adiponectin which may have an influence on the pathogenesis of GERD.

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