Reports of Biochemistry & Molecular Biology
Vol.8, No.3, Oct 2019

Original article

www.RBMB.net

E-Cadherin Protein as a Potential Marker for Gastric Cancer and Its Association with *Helicobacter Pylori*- Induced Gastritis and Gastric Ulcer

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Abstract

Background: Gastric cancer is still the main health threat being the third leading cause of deaths from cancers in the world. The major risk behind the gastric cancer is that it remains asymptomatic in the early stages and in (97%) cases it metastasizes to other organs. Gastric cancer is a multifactorial disease in which *Helicobacter pylori* (*H. pylori*) has been known as a risk factor. However, patients with gastritis, especially atrophic gastritis and gastric ulcer have been shown to be at an increased risk for developing gastric cancer.
Methods: This study included measuring the serum levels of E-Cadherin protein, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) in 30 patients diagnosed with gastritis, 20 gastric ulcer patients, 20 gastric cancer patients and in 20 healthy volunteers serving as the control group.
Results: Infection with *H. pylori* was diagnosed by serology (IgA and IgG antibodies) as well as by rapid urease test (RUT) and histology. The results showed that 50 (71.4%) of the patients were positive for *H. pylori*. Levels of E-Cadherin were increased significantly in all patients in comparison to the control group with a large significant increase in the gastric cancer group. The levels of E-Cadherin were also significantly increased in *H. pylori* infected patients compared to *H. pylori* negative patients. A non-significant difference in the levels of CA19-9 and CEA was observed in all patients in comparison to healthy controls.
Conclusions: This study concluded that serum E-Cadherin could be considered as a potential marker in diagnosis of gastric cancer.

Keywords: E-Cadherin, Gastric Cancer, Gastric Ulcer, Gastritis, *Helicobacter Pylori*.

Introduction

Stomach cancer also referred to as gastric cancer is defined as any malignancy arising from the region between the gastroesophagus junction and the pylorus. Stomach cancer comes in the third place regarding deaths from cancer and a significant global threat to public health (1, 2). From this prospective the early diagnosis of stomach cancer is extremely important. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) tumor markers have been widely used for the diagnosis of gastric cancer, however, a very large amount of previous trials was performed about the value of these tumor markers as diagnostic tools and the results were mostly contradictory but the majority of studies have concluded that CEA and CA19-9 tumor markers are not reliable nor accurate tools in the detection of stomach cancer in its initial stages as well as other types of cancers (3–7). While stomach cancer etiology is multifactorial, more than 80 percent of the cases are due to *H. Pylori* Infection. Furthermore, gastric carcinogenesis is contributed also by diet, lifestyle, genetic, social and other factors. Based on research data that have shown that *H. pylori* is a basic requirement of gastric cancer. The WHO categorized *H. pylori* as a (class 1 carcinogen) (8–

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Received: 7 May, 2019; Accepted: 12 May, 2019

11). The mature protein E-cadherin is a 120 kDa transmembrane glycoprotein and the functional protein relies on Ca^{2+} binding. This protein connects normal and polarized epithelial cells with each other by the formation of adherens junctions (AJs). The E-cadherin amino terminal has five extracellular cadherin sites and each site (domain) binds a Ca^{2+} ion, this site-calcium binding is responsible for the adhesion characteristics of the protein. The binding of Ca^{2+} ions promotes and infers resistance to the action of proteases. These extracellular binding patterns are crucial for the formation of the three dimensional, functionally active protein (12). The E-cadherin glycoprotein consists of three primary infrastructural areas: a single transmembrane domain, linked to a cytoplasmic field, and a single non-membrane (extracellular) domain consisting of five succession-repetitious domains, EC1–EC5, exclusive to the cadherins. For the appropriate folding of proteins as well as the adherence of the cells, the extracellular site of E-cadherin is crucial. E-cadherin's cytoplasmic site comes into contact with the catenins of the cytoskeleton actin (α-, β-, γ- and p120), this process forms the basis of the AJs (13, 14). Since it is the prime facet of the AJs, E-cadherin is indispensable for cell contacts of the epithelial cells of the stomach. Hence, lowering of E-cadherin understandably alludes to propagation of stomach diseases and further carcinoma advancement (15, 16). Gastric cancer advances during a series of very well characterized histological steps. It starts by the shift from the completely normal mucosa to superficial gastritis, then, atrophic gastritis and intestinal metaplasia follows, this may or may not be preceded by gastric ulcer. At last, this process leads to dysplasia and adenocarcinoma (17, 18). Accordingly, in this study, the E-Cadherin level was measured in the sera of patients with gastric related diseases, this might give some information or knowledge about the formation of gastric cancer from previous gastritis and/or gastric ulcers. This approach may reflect the role of E-Cadherin protein in the development of gastric cancer and might even propose a possible better method for the diagnosis of gastric cancer.

Materials and methods

Study subjects

Seventy patients and twenty healthy individuals were enrolled in this study. The subjects enrolled in the present study were attending the educational oncology hospital, medical city, Baghdad, the endoscopy unit of gastroenterology and liver diseases hospital, medical city, Baghdad and the endoscopy unit of azadi teaching hospital, Duhok. This study was approved by the Department of Chemistry, College of Science, Al-Mustansiriyah University, Baghdad, Iraq, the Iraqi Ministry of Health and by the Research Ethics Committee of Duhok Directorate General of Health, Kurdistan Regional Government, Iraq. The patients were grouped according to their clinical diagnosis; 20 patients with gastric cancer (eight females and twelve males), age (37–74 and 59–85 years respectively). Twenty patients with gastric ulcer (10 females and 10 males), age (19–60 and 14–60 years respectively). Thirty patients with gastritis (16 females and 14 males), age (18–55 and 17–40 years respectively). This study also included twenty healthy subjects (10 females and 10 males), age (22–41 and 18–47 years respectively) serving as the control group.

Exclusion criteria

The following criteria were applied in excluding cases, since they may have an effect on the results of the study; if the patient was under or had a previous chemotherapy, if the patient was under a current antibiotic or PPI treatment, or had a previous antibiotic treatment less than 6 months from the time of blood collection, if the patient was using Nonsteroidal anti-inflammatory drugs (NSAID) drugs, If the patient had another type of cancer, if the patient had a liver inflammation or other related liver diseases, if the patient went through any type of gastrectomy, and if any of the healthy subjects (controls) were infected with *H. Pylori*.

Samples collection

Ten milliliters of blood were taken from the patients and healthy control. Blood samples were transferred into gel tubes and they were left for 15-30 minutes at room temperature to clot. The obtained serum samples were stored at (-20 ºC) till

assayed. In addition, biopsy samples removed from the stomach of patients by the doctors performing the endoscopy were also collected for histology and rapid urease test (RUT).

Histology and rapid urease test (RUT)

Histology was performed by specialized histologists in the laboratories of each hospital from which the biopsies were taken. RUT was performed in the endoscopy unit during the endoscopy procedure. A biopsy from the antrum were combined with a biopsy from the corpus and were placed on the RUT cassette and covered. After one hour, a color change (from yellow to pink) indicated a positive test.

Biochemical analysis

Serum E-Cadherin was measured by enzyme linked immunosorbent assay (ELISA) using Human E-Cadherin Elisa Kit provided by (Mybiosource/ USA) following the kit's directions Anti-*H. pylori* IgG and IgA antibodies were measure by ELISA using *Helicobacter* IgG Elisa Kit and *Helicobacter* IgA Elisa Kit provided by (Demeditec/ Germany) following the kit's directions. CEA and CA 19-9 tumor markers were measured by enzyme linked fluorescent assay (ELFA) using VIDAS CEA (S) and VIDAS CA 19-9 (199) kits provided by (Biomerieux/ France) following the kit's directions.

Statistical analysis

Biochemical data were analyzed using SPSS (statistical package for social sciences) version 25. T-Test was used to calculate mean ± standard deviation (SD) and the p value.

Results

H. pylori infection

Infection with *H. pylori* was diagnosed by anti-*H. pylori* IgG and IgA antibodies (serology) as well as by RUT and histology. The results showed that a total of 50 (71.43%) subjects had a positive *H. pylori* test and 20 (28.57%) of the subjects were negative. The results of the control group were all negative. The subject was accounted to be positive for *H. pylori* if a minimum of two tests showed positive results. Tables (1) and (2) show the status of the infection of each group in this study and the results of each diagnostic method compared with the others respectively.

Table 1. Helicobacter pylori status of patients and control groups

Groups	*H. pylori* Positive N (%)	*H. pylori* Negative N (%)
Gastric Cancer Total N = 20	7 (35)	13 (65)
Gastric Ulcer Total N = 20	13 (65)	7 (35)
Gastritis Total N = 30	30 (100)	0 (0)
Control Total N = 20	0 (0)	20 (100)

Table 2. Results of Helicobacter pylori diagnostic methods

Diagnostic Method	Positive Cases N (%)	Negative Cases N (%)
Patients N = 70	50 (71.4)	20 (28.6)
Histology	50 (71.4)	20 (28.6)
RUT	50 (71.4)	20 (28.6)
IgG	59 (84.3)	11 (15.7)
IgA	11 (15.7)	59 (84.3)
Control N = 20	0 (0)	20 (100)
IgG	0 (0)	20 (100)
IgA	0 (0)	20 (100)

The first method to be used to diagnose *H. pylori* was histology and is considered the standard gold method (19). The RUT works by a principle that *H. pylori* produces huge quantities of the urease enzyme, which in turn reacts to form ammonia with the urea test reagent, enabling it to be detected by a rapid indirect test. performance of histology and RUT diminishes with partial or complete gastrectomy as well as with bleeding from peptic ulcers, antibiotics, proton pump inhibitors (PPIs), bismuth compounds, (20, 21), pathologist's experience, and reading the RUT earlier than the time recommended by the test may result in false negative results (22–24). Forceps contaminated with formalin also cause the sensitivity to decrease (25). Several studies concluded that, in addition to increasing the number of biopsies, the collection of biopsies from different regions of the stomach could result in a higher accuracy of both histology and the RUT (19, 23, 26). Our serological tests are almost in accordance to many other previous studies performed on evaluating the diagnostic accuracy of IgG and IgA antibodies. Studies also showed that IgA based serologic tests were much less useful and less accurate in contrast to IgG based tests which showed sensitivities up to (100%) and specificities of (58–97%) supporting that IgG tests are more accurate and reliable (27–29). For these findings, one possible explanation is that *H. pylori* Infection is basically an inveterate situation (24), thus the systemic reaction begins with an elevation in IgM and an increase in IgA and IgG antibodies follows. High levels of IgG are seen in nearly all individuals with *H. pylori* infection, but IgA levels exceed cut-off values in only about two thirds of cases (30). Serological tests are generally relatively cheap, performed quickly and, unlike invasive methods, cause minimal discomfort to the patient (31). Still, these tests are not useful in evaluating eradication therapy because, these tests cannot differentiate active (current) infection from past (inactive) infection, which make these tests unreliable in solely diagnosing *H. pylori* (31, 32).

Biochemical analysis

Tables (3 and 4) show the levels of serum E-Cadherin, CA 19-9 and CEA in the study subjects. Table (5) shows the serum levels of E-Cadherin, CEA and CA 19-9 in patients infected with *H. pylori* in comparison to uninfected patients.

Table 3. Levels of serum E-Cadherin, CA 19-9 and CEA in the study subjects.

Parameters	(A) Gastric Cancer Mean ± SD	(B) Gastric Ulcer Mean ± SD	(C) Gastritis Mean ± SD	(D) Control Mean ± SD	p-value A vs D	p-value B vs D	p-value C vs D
E-Cadherin (pg/mL)	7812.75 ± 684.975	6010.71 ± 287.729	5216 ± 397.29	4133.94 ± 324.36	0.000	0.000	0.000
CEA (ng/mL)	3.96 ± 1.93	3.77 ± 1.64	3.62 ± 1.42	2.98 ± 1.41	0.094	0.135	0.147
CA 19-9 (U/mL)	17.68 ± 17.04	14.40 ± 9.13	13.94 ± 7.74	13.03 ± 8.35	0.313	0.642	0.708

*significant at the level of ($p \leq 0.05$)

Table 4. Levels of serum E-Cadherin, CA 19-9 and CEA in patients' groups

Parameters	(A) Gastric Cancer Mean ± SD	(B) Gastric Ulcer Mean ± SD	(C) Gastritis Mean ± SD	p-value A vs B	p-value A vs C	p-value B vs C
E-Cadherin (pg/mL)	7812.75 ± 684.975	6010.71 ±287.729	5216 ± 397.29	0.000	0.000	0.000
CEA (ng/mL)	3.96 ± 1.93	3.77 ± 1.64	3.62 ± 1.42	0.743	0.484	0.740
CA 19-9 (U/mL)	17.68 ± 17.04	14.40 ± 9.13	13.94 ± 7.74	0.464	0.308	0.852

*significant at the level of ($p \leq 0.05$)

Table 5. Levels of serum E-Cadherin, CA 19-9 and CEA in *H. pylori* infected subjects.

Parameters	Gastric Cancer (Mean ± SD)		p-value	Gastric Ulcer (Mean ± SD)		p-value
	HP +	HP -		HP +	HP -	
E-Cadherin (pg/mL)	8580.21 ± 385.21	7399.5 ± 343.38	0.000*	6481.04 ± 204.99	5993.07 ± 61.05	0.000*
CEA (ng/mL)	3.90 ± 1.02	3.99 ± 2.27	0.929	3.56 ± 1.18	4.15 ± 2.21	0.472
CA 19-9 (U/mL)	16.66 ± 11.73	18.14 ± 19.29	0.853	14.56 ± 9.45	14.07 ± 8.49	0.912

HP: *H. pylori*. *significant at the level of ($p \leq 0.05$)

Discussion

E-cadherin's extracellular site is proteolytically, cleaved by pathologic effects like *H. pylori*, with MMPs (matrix metalloproteinases), KLK7 (callikrein-linked peptidase) and ADAMs (disintegrin metalloproteinases) in the stomach epithelial cells (33). E-cadherin's proteolytic cleavage produces an 80 kDa remnant, which leaks into general circulation. This E-cadherin remnant is called soluble E-cadherin (12, 34). This cleavage leads to the disassembly of the adherens junctions leading to the aggregation of the β-catenin and catenin-δ-1 in the cytoplasm (35–37). This gives a possible explanation for the results of the current study. Only few studies were performed regarding the soluble E-Cadherin and the majority of these studies support this study's findings. The first study reported that soluble E-Cadherin concentrations were elevated in (22) patients with gastric cancer patients compared with non-tumor controls (38), and it was further supported by another study in a larger sample size (N =81) (39). Another study measured the E-Cadherin serum concentrations in three cancers; gastric, colorectal and breast, they showed that the E-Cadherin concentrations were greater in gastric cancer (40). Many studies have described the role of E-Cadherin as a prognostic factor for gastric cancer and showed that soluble E-Cadherin elevated concentrations may predict a T4 stage tumor with depth invasion and poor survival (41–43). A study also showed that increased levels of soluble E-cadherin in serum from 3 to 6 months can anticipate reoccurrence of gastric adenocarcinoma after healing surgery (44). An Egyptian study showed that soluble E-Cadherin levels were elevated in gastritis patients and more elevated in patients with gastric cancer in comparison to the healthy subjects (45). This shows that soluble E-cadherin may act as a potential biomarker for gastric cancer detection, prediction and reoccurrence (46). However, one study in the United Kingdom showed that E-cadherin levels were not increased in patients with gastric cancer in comparison to the control group (47). In addition, a study in Poland on colorectal cancer patients showed that there was no significance difference in the concentration of soluble E-Cadherin between the patients and healthy controls (48).

The majority of studies have concluded that CEA and CA 19-9 tumor markers are not reliable nor accurate tools for the diagnosis of stomach cancer. The results of the present study are in accordance to the previous studies. Some studies have suggested that CA 19-9 and CEA are useful tools in surveilling reoccurrence and metastasis, in addition to the effectiveness of chemotherapy and prediction of stomach cancer (49, 50). Multiple studies have said that the CA 19-9 and the CEA were not satisfactory tools for screening and diagnosing stomach cancer in its initial stages (50–55), however. Several studies have found that these markers have been increased in other tumors and non-malignant diseases including gastritis, peptic ulcer, duodenitis, oesophagitis, diverticulitis, chronic obstructive pulmonary disease, diabetes and any acute, or chronic inflammatory disease (56–60). Moreover, certain surveys have shown that the benefits of CEA and CA 19-9 are in doubt even as markers of surveillance in stomach cancer (61–63). In summary, the functioning of gastric mucosa is influenced greatly by E-cadherin since it is the primary member of the AJs responsible for adhesion and integrity of the cells in the stomach. The dysregulation of E-Cadherin reflected in its

high levels found in sera of patients may indicate the extent of damage done to the gastric mucosa. The high concentrations of E-Cadherin found in gastric cancer patients may indicate severe damage or defects in the gastric mucosa while the somewhat lower concentrations of E-Cadherin found in gastritis and gastric ulcer patients can indicate lower defects or damage in the gastric mucosa, still this may lead to a conclusion that gastritis and gastric ulcer patients are both at higher risk for developing gastric cancer if remained untreated and one possible option is the eradication of *H. pylori* since it was shown that this bacterium has a pronounced effect in the development of gastric related conditions or diseases which was reflected in the higher levels of E-Cadherin in *H. pylori* positive patients. Thus, serum levels of E-Cadherin can predict gastric cancer as well as discriminate it from gastric ulcer and gastritis even before performing endoscopy. CA 19-9 and CEA cannot differentiate gastric cancer from gastric ulcer and/or gastritis. In addition, the levels are considered within the normal range meaning that the positive rate for both markers are very low and they possess low sensitivities and specificities.

E-Cadherin protein may act as a probable marker in the diagnosis of gastric cancer. CA 19-9 and CEA are not reliable in the screening for gastric cancer. *H. pylori* possess a marked influence on the development of gastric cancer. Gastritis and gastric ulcer patients could be at a higher danger for the development of gastric cancer.

Acknowledgment

The work was supported by the Department of Chemistry and Department of Biology in the College of Science at Mustansiriyah University in Baghdad, Iraq.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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