

## Insulin Resistance Is Associated with Early Gastric Cancer: A Prospective Multicenter Case Control Study

Hye Jung Kwon<sup>1</sup>, Moo In Park<sup>1</sup>, Seun Ja Park<sup>1</sup>, Won Moon<sup>1</sup>, Sung Eun Kim<sup>1</sup>, Jae Hyun Kim<sup>1</sup>, Youn Jung Choi<sup>1</sup>, and Sang Kil Lee<sup>2</sup>

<sup>1</sup>Division of Gastroenterology, Department of Internal Medicine, Kosin University College of Medicine, Busan, and <sup>2</sup>Division of Gastroenterology, Department of Internal Medicine, Institute of Gastroenterology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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**Background/Aims:** Recently, increased body weight has been found to be associated with an increasing risk of several cancers, including gastric cancer. The true pathogenic role of hyperglycemia in the development of gastric cancer remains unclear as hyperglycemia and its associated conditions may work as carcinogenic factors. The goal of this study was to clarify the factors associated with early gastric cancer and evaluate a homeostasis model assessment of the insulin resistance (HOMA-IR) index, fasting glucose, and lipid profile as predictors of early gastric cancer. **Methods:** A total of 63 patients with early gastric cancer between November 2012 and March 2013 were included. Preoperative serum lipid profile levels and serum fasting glucose were examined prospectively in patients with early gastric cancer. The same number of controls were evaluated and matched to the early gastric cancer group for age and gender. We performed multivariate logistic regression analysis to identify independent risk factors for early gastric cancer. **Results:** Univariate analysis showed that risk for early gastric cancer was associated with diastolic blood pressure (BP), total cholesterol, fasting glucose, and HOMA-IR. In the multivariate-adjusted model, higher total cholesterol, fasting glucose, body mass index, and diastolic BP were strongly associated with an increased risk of early gastric cancer. **Conclusions:** Hyperglycemia, a lower high-density lipoprotein cholesterol level, and a low HOMA-IR level appear to be associated with early gastric cancer risk. (*Gut Liver* 2019;13:154-160)

**Key Words:** Early gastric cancer; Hyperglycemia; HOMA-IR; Adiponectin; Cholesterol

### INTRODUCTION

Gastric cancer is one of the most common causes of cancer induced deaths. Because of the survival of patients that have advanced gastric cancer is almost poor, early detection, and proper resection of the gastric malignant lesion at an earlier stage improves the survival.<sup>1-3</sup> More effective approach for surveillance of early gastric cancer (EGC) is needed. Various studies have improved that *Helicobacter pylori* infection is obvious risk factor for the carcinogenesis of stomach.<sup>4</sup> However in addition to infection of *H. pylori*, multiple cofactors would play a role in gastric carcinogenesis. There were many evidences prove that patients of diabetes mellitus (DM) had a higher risk of cardiovascular disease and malignancies in various organs.<sup>5-8</sup> Nevertheless, few studies had focused on the relationship between DM, hyperglycemic state and the development of EGC.<sup>9</sup> Authors have a question as to whether the development of EGC is related to insulin resistant state, not overt DM.

Recently, there has been a study that adiponectin, one kind of adipokine, was elevated in advanced gastric cancer.<sup>10,11</sup> The adiponectin is associated with the pathogenesis of DM through the regulation of glucose, metabolism of fatty acid, and insulin sensitivity in various epithelial and stromal cells.<sup>12,13</sup> We measured it in a Korean population and examined the relationship between the development of EGC and plasma adiponectin levels.

In this study, we evaluated insulin resistance (fasting glucose, fasting insulin, glycated hemoglobin [HbA1c], homeostasis model assessment of the insulin resistance [HOMA-IR], and HOMA  $\beta$ -cell function), lipid profile (total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglyceride [TG]) and plasma level of adiponectin in EGC patients and examined a possible role for adipokines in the development

Correspondence to: Moo In Park (<https://orcid.org/0000-0003-2071-6957>)

Division of Gastroenterology, Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea  
Tel: +82-51-990-6103, Fax: +82-51-990-5055, E-mail: mipark@ns.kosinmed.or.kr

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of EGC.

## MATERIALS AND METHODS

### 1. Patients

This study is a case control prospective study performed in two centers (Kosin University Gospel Hospital and Yonsei Severance Hospital), from October 1, 2012 to March 31, 2013. We performed sample size assessment and determined that a total of 194 participants were needed, 97 in each group (EGC and controls). The inclusion criteria were aged between 18 to 75 years old with written informed consent. The EGC group included patients who underwent endoscopic submucosal dissection or gastrectomy with conventional lymph node dissection and received pathological diagnosis of EGC. The control group was matched for age and sex (1:1) to the EGC group and subjects were enrolled from the health promotion center of each hospital. Subjects in both groups were excluded if they had any active malignancies (except gastric cancer for the EGC group) or a past history of any other malignancies. Exclusion criteria were patients with peptic ulcer disease or gastroesophageal reflux disease, oral hypoglycemic agents or insulin users due to diabetes, and patients taking oral lipid lowering agents due to hypercholesterolemia. Study protocol was reviewed and approved by the Institutional Review Board (IRB No. KAIRB 13-152).

### 2. Assessment of study protocol

Clinical and pathological information of all subjects were obtained from medical records. The body mass index (BMI) at the time of diagnosis was calculated based on weight (kg)/height (m)<sup>2</sup>. Subjects (EGC and control group) were provide informed consent prior to the collection and analysis of blood samples.

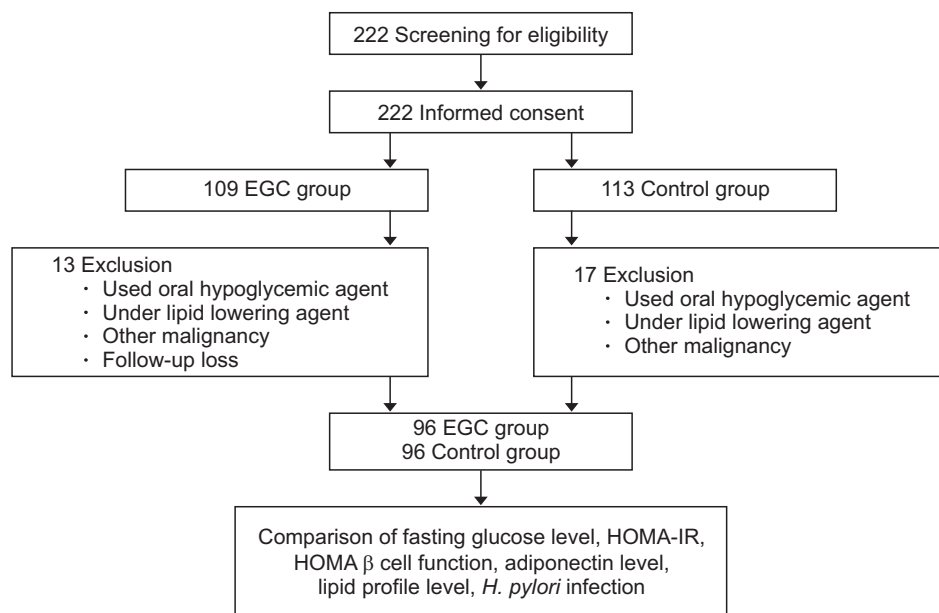
Serum was collected from all subjects after overnight or 12 hours of fasting time. We requested that each subject be provided with a 10 mL blood sample at the time of admission or health checkup. The collected blood samples were stored at -80°C until analysis.

Several parameters were measured that fasting glucose, HbA1c, and fasting insulin. We also investigated HOMA-IR and HOMA  $\beta$ -cell function as a value reflecting insulin resistance. The HOMA-IR score was calculated by the formula: (fasting insulin [ $\mu$ U/mL] $\times$ fasting glucose [mmol/L])/22.5. HOMA-IR  $\geq$ 1.96 was defined as the presence of insulin resistance<sup>5</sup> HOMA  $\beta$ -cell function was calculated by the formula: (20 $\times$ fasting insulin [ $\mu$ U/mL])/(fasting glucose [mmol]-3.5).<sup>5,14</sup> Serum TC, TG, HDL and LDL values were determined by enzymatic methods.

Plasma adiponectin levels were measured using an adiponectin ELISA kit (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan). The adiponectin concentration was divided into two classes: The level of Adiponectin  $\geq$ 8.0 ng/dL and <8.0 ng/dL.<sup>15</sup> *H. pylori* infection status was considered positive if the subjects had either *H. pylori* antibody  $\geq$ 10 U/mL.<sup>15</sup>

### 3. Statistical analysis

For continuous variables, the results expressed as mean $\pm$  standard deviation or median. The Student t-test and chi-square test were used to compare basic characteristics between the EGC and control groups. Matched odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using logistic regression models. p-values less than 0.05 were defined as statistically significant. All statistical analyses were performed with SPSS version 8.0 (SPSS Inc., Chicago, IL, USA).



**Fig. 1.** Study flowchart. EGC, early gastric cancer; HOMA-IR, homeostasis model assessment of the insulin resistance; *H. pylori*; *Helicobacter pylori*.

## RESULTS

From November 2012 to March 2013, we initially recruited a total of 222 participants. Among them, 13 participants in the EGC group were excluded because of use of oral hypoglycemic agents or lipid lowering agents or the presence of other malignant disease. An additional 17 participants were excluded from the control group because of the presence of another malignant disease. We therefore included 96 individuals in the EGC group and control group, respectively, according to inclusion criteria. The study flow showed Fig. 1. Each group included 66 men and 30 women. Table 1 shows the basic characteristics of the two groups. There was no difference in height, weight, and BMI between the two groups, and the mean age was 55.6 years. The rate of *H. pylori* infection was higher in the EGC group than the control group. There were no statistically significant differences in the rate of alcohol consumption and smoking between groups. Fasting glucose, fasting insulin, HOMA-IR, HbA1c, TC, HDL, and diastolic blood pressure were statistically significant in the EGC group compared with control group. Although this difference was not statistically significant, serum level of adiponectin was lower in the EGC group (Table 1). The univariate analyses showed that risk of cancer was slightly increased

among persons with a higher level of fasting glucose, fasting insulin, HOMA-IR, HbA1c, and a lower level of TC and HDL. *H. pylori* infection was a significant risk factor in the EGC group ( $p=0.003$ ). BMI, HOMA  $\beta$ -cell function, LDL, TG level, and adiponectin concentration were not associated with the risk of EGC development in this study (Table 2). The multivariate logistic regression analysis showed that high level of fasting glucose (OR=1.08,  $p<0.01$ ), high level of fasting insulin (OR=1.69,  $p=0.02$ ), HOMA-IR (OR=8.85,  $p=0.03$ ), and lower level of TC (OR=1.01,  $p=0.005$ ) were associated with the development of EGC (Table 3). HDL level was not affected in multivariate analysis.

## DISCUSSION

This is prospective, population-based study to report a positive association between insulin resistance and development of EGC in the absence of overt DM. This prospective study provided several salient findings. First, hyperglycemia ( $p=0.000$ , OR=1.066) and insulin resistance (fasting insulin [ $p=0.024$ , OR=1.084], HOMA-IR [ $p=0.006$ , OR=1.532] and HbA1C [ $p=0.004$ , OR=3.225]) were risk factors for the development of EGC. Second, a low level of TC ( $p=0.005$ , OR=1.015) was associated with the development of EGC. Third, although plasma adiponectin level was lower in EGC group, but there was no statistical significance. In a recent study, Ikeda *et al.*<sup>16</sup> reported that hyperglycemia (fasting glucose  $\geq 5.3$  mmol/L) increased the risk of gastric cancer induced by *H. pylori* infection. Similar to their data, our prospective case control study demonstrated that the presence of hyperglycemia, hyperinsulinemia and elevated HOMA-IR were significantly related to the development of EGC based on multivariate analyses. A previous study showed that the incidence of gastric cancer is greater in patients with a higher level of HbA1C,<sup>17</sup> and our data support this relationship ( $p<0.01$ , OR=1.08). As the previous studies included AGC, it could not rule out secondary hyperglycemia as cancer progress. This study targeted EGC only excluding other variables, which makes higher possibility of EGC acting as main cause. There have been several studies dealing with relevancy between gastric dysplasia and hyperglycemia but this is the first time studying for EGC only. We also investigated plasma fasting insulin, calculated HOMA-IR and HOMA  $\beta$ -cell function that reflect insulin resistance.<sup>5,13</sup> Among them, fasting insulin ( $p=0.02$ , OR=1.69) and HOMA-IR ( $p=0.03$ , OR=8.85) were confirmed to contribute to the development of EGC.

Why does gastric cancer development occur more common in hyperglycemic state than in without hyperglycemia? The exact pathophysiological role of hyperglycemia in the development of stomach cancer remains to be unclear but several possible mechanisms have been suggested. The production of oxygen free radicals that cause DNA damage<sup>18</sup> increases in hyperglycemic state. High levels of glucose have been shown to contrib-

**Table 1.** Baseline Patient Characteristics of Early Gastric Cancer and Control Groups

Characteristic	EGC (n=96)	Control (n=96)	p-value
Age, yr	55.6 $\pm$ 11.73	55.6 $\pm$ 11.73	0.021
Sex, male/female	66/30	66/30	
BMI, kg/m <sup>2</sup>	23.80 $\pm$ 2.90	24.30 $\pm$ 2.42	0.195
SBP, mm Hg	124.7 $\pm$ 12.80	123.6 $\pm$ 9.87	0.500
DBP, mm Hg	79.08 $\pm$ 7.67	75.42 $\pm$ 7.39	0.009
AC, cm	81.77 $\pm$ 7.57	83.08 $\pm$ 8.069	0.297
Total cholesterol, mg/dL	179.3 $\pm$ 35.47	196.2 $\pm$ 35.61	0.001
HDL, mg/dL	46.83 $\pm$ 11.46	51.48 $\pm$ 12.28	0.007
LDL, mg/dL	104.5 $\pm$ 33.62	112.5 $\pm$ 33.89	0.102
Triglyceride, mg/dL	129.8 $\pm$ 71.84	139.7 $\pm$ 136.5	0.529
TG/HDL index	3.09 $\pm$ 2.17	3.26 $\pm$ 5.39	0.773
Fasting glucose, mg/dL	98.61 $\pm$ 15.89	87.41 $\pm$ 13.30	0.001
Fasting insulin, mg/dL	6.27 $\pm$ 7.09	4.33 $\pm$ 3.16	0.015
HOMA-IR	1.56 $\pm$ 1.71	0.96 $\pm$ 0.75	0.002
HOMA $\beta$ -cell	1.30 $\pm$ 0.46	1.28 $\pm$ 0.45	0.752
Adiponectin, ng/mL	8.28 $\pm$ 4.98	8.61 $\pm$ 6.23	0.685
HbA1C, %	5.82 $\pm$ 0.47	5.63 $\pm$ 0.38	0.002

Data are presented as mean $\pm$ SD or number.

EGC, early gastric cancer; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AC, abdominal circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; HOMA-IR, homeostasis model assessment of the insulin resistance; HbA1C, glycated hemoglobin.

**Table 2.** Univariate Logistic Regression Analysis for the Risk of Early Gastric Cancer

Variable	EGC (n=96)	Controls (n=96)	OR (95% CI)	p-value
BMI, kg/cm <sup>2</sup>			0.931 (0.837–1.037)	0.1957
<18.5	4	0		
18.5–25	66	60		
≥25	26	36		
FBS, mg/dL			1.066 (1.037–1.096)	0.0001
<100	60	89		
≥100	36	7		
Fasting insulin, mg/dL			1.084 (1.011–1.162)	0.0243
<6.20	70	73		
≥6.20	26	23		
HOMA-IR			1.532 (1.134–2.071)	0.0055
<1.96	75	85		
≥1.96	21	11		
HOMA β-cell function			0.904 (0.485–1.685)	0.7508
<1.18	67	69		
≥1.18	29	27		
HbA1C			3.225 (1.455–7.147)	0.0039
<6.0	71	84		
≥6.0	25	12		
Adiponectin, ng/dL			0.99 (0.941–1.041)	0.6847
<8.0	53	61		
≥8.0	43	35		
Total cholesterol, mg/dL			0.987 (0.978–0.995)	0.0018
<200	68	60		
200–239	25	25		
≥240	3	11		
HDL, mg/dL			0.967 (0.943–0.992)	0.0089
<40	30	17		
≥40	63	79		
LDL, mg/dL			0.993 (0.984–1.001)	0.1042
<100	49	35		
100–129	26	37		
130–159	17	13		
≥160	4	11		
Triglyceride, mg/dL			0.999 (0.996–1.002)	0.5363
<150	73	69		
≥150	23	27		
<i>H. pylori</i> infection			-	0.003
Positive	76	57		
Negative	20	39		

EGC, early gastric cancer; OR, odds ratio; CI, confidence interval; BMI, body mass index; FBS, fasting blood sugar; HOMA-IR, homeostasis model assessment of the insulin resistance; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *H. pylori*, *Helicobacter pylori*.

ute to DNA damage in hyperglycemic patients.<sup>19</sup> To the next, hyperinsulinemia itself is another possible mechanism of the

development of gastric malignancy. Insulin is a key regulator of carcinogenesis in several organs including gastric cancer.<sup>20-23</sup>

**Table 3.** Multivariate Logistic Regression Analysis for the Risk of Early Gastric Cancer

Variable	$\beta$	SE	p-value	OR (95% CI)
DBP	-0.920	0.030	0.002	0.912 (0.860-0.967)
Total cholesterol	0.015	0.005	0.005	1.015 (1.005-1.026)
HDL	-0.018	0.016	0.263	0.982 (0.952-1.013)
Fasting glucose	0.084	0.024	0.001	1.088 (1.037-1.141)
Fasting insulin	0.525	0.233	0.025	1.690 (1.069-2.670)
HOMA-IR	2.181	1.019	0.032	8.853 (1.201-65.25)
HbA1C	0.721	0.514	0.160	2.057 (0.752-5.629)

SE, standard error; OR, odds ratio; CI, confidence intervals; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of the insulin resistance; HbA1C, gly-cated hemoglobin.

Insulin may improve the bioavailability of insulin like growth factor 1 (IGF-1) by inhibiting the production of IGF-binding proteins.<sup>21,22</sup> Bioavailable IGF-1 and insulin signal transduction develop pass through insulin, IGF-1, and hybrid receptors in the cell membrane.<sup>21,23</sup> Inhibition of apoptosis, stimulation of cellular proliferation and carcinogenesis develop because of a number of downstream pathways activated by these receptors. Despite these possible mechanisms, further studies needed to clear the pathophysiological role of hyperglycemia and insulin resistance in gastric carcinogenesis.

This study was able to more accurately survey the effects of insulin resistance in EGC by minimizing confounding factors such as BMI, AC, age, and sex. Identification of risk factors that precede the development of EGC can inform strategies to prevent EGC. Although several studies have evaluated the association between insulin resistance and gastric cancer, this study focused on EGC and possible associations with hyperglycemia and insulin resistance. In a recent study, it was found that there was inverse correlation between serum cholesterol levels and the incidence of gastric cancer, especially intestinal type.<sup>23,24</sup> It is generally accepted that intestinal type cancer develops by a multistep leading to chronic active gastritis, gastric atrophy process and intestinal metaplasia from normal gastric mucosa and finally to dysplasia and cancer.<sup>25</sup> These steps include the inflammatory process through activation of the pro-inflammatory transcription factor, nuclear factor  $\kappa$ B (NF- $\kappa$ B).<sup>26</sup> Cholesterol is an important structural lipid that required to maintain cell function.<sup>27</sup> An experimental study showed that long term deficiency of serum cholesterol induces NF- $\kappa$ B activation, which could promote tumorigenesis.<sup>28</sup> Accordingly, we investigated serum lipid profiles related to the development of EGC. Among serum lipid profiles, only TC ( $p=0.005$ , OR=0.985) was an independent risk factor in our study. In univariate analysis showed that HDL ( $p=0.009$ ) was statistically significant factor, but not in multivariate analysis. Although cholesterol level is affected by dietary factors and several co-factors, the above mentions would somehow support our results.

Adiponectin is one of the active adipokines involved in the pathogenesis of diabetes through regulation of glucose and fatty acid metabolism and insulin sensitivity in various stromal or epithelial cells.<sup>29-31</sup> Excess adiposity, including visceral obesity, results in a state of chronic systemic low grade inflammatory state due to the production of inflammatory cytokines by both adipocytes and invasive immune cells, creating a pro-tumorigenic environment.<sup>32</sup> On the contrary, the circulating level of adiponectin is inversely correlated the risk of some cancers related to body mass index,<sup>29</sup> and some polymorphisms of adiponectin and its receptor genes are correlated the risk of cancers.<sup>33</sup> Many studies indicate that adiponectin has anticancer effects and plays an important role in the development and progression of obesity related malignant tumors.<sup>33-36</sup> Ishikawa *et al.*<sup>37</sup> recently reported that low plasma adiponectin concentrations are correlated an increased risk of gastric cancer and adiponectin is potentially involved in the progression of gastric cancer in especially in undifferentiated type cancers of the upper stomach. In a Nakajima *et al.*<sup>38</sup> comparing 38 patients with Stage I gastric cancer and controls, adiponectin tended to decrease in cancer patients ( $p=0.0582$ ), but the difference was not statistically significant. Based on these previous studies, we investigated the relationship of plasma adiponectin and the development of EGC, excluding AGC. Plasma adiponectin tended to be lower in the EGC group ( $8.28\pm 4.98$  ng/mL) than in to control group ( $8.61\pm 6.23$  ng/mL), but the difference was not statistically significance. Plasma adiponectin could not be used as a conclusive biomarker for the detection of EGC in our study. However, based on these recent studies low plasma adiponectin levels are correlated an increased risk for gastric cancer and it is likely that adiponectin may play a potential role in cancer progression,<sup>39-42</sup> further larger scale, well-designed studies are needed to confirm this connection.

This is the first study to examine the relationship of hyperglycemia, insulin resistance, lipid profile and adiponectin in EGC alone, excluding AGC. We revealed that elevated fasting glucose and fasting insulin, HbA1c, HOMA-IR, and serum TC were independent risk factors of the development of EGC. Furthermore, general population with hyperglycemia or other elevated glycemic markers, should be advised to recommend appropriate gastric cancer screenings or surveillance even in the absence of obesity or diabetes.

These are also limitations to this case-control study. First, the average glucose levels were within normal range in both two group (98.61 vs 87.41). Although EGC group and Control group was not diagnosed overt DM and there was statistical significance, it was not hyperglycemia, not even impaired glucose tolerance of impaired fasting glucose. Although interpretation of results may be a logical leap, but insulin resistance is time consuming and sequential events. As well as obesity and *H. pylori* infection, gastric carcinogenesis appear to be confounded by presence of shared cancer promoting or preventing factors. It

is difficult to accurately assess gastric cancer risk in subjects because of these confounding factors. Thus, investigation into the substantial gastric cancer risk in participants requires adjustment based on these confounding factors. Therefore, well-designed large scale prospective epidemiological studies are needed to confirm the association between diabetes and gastric carcinogenesis in humans. In conclusion, hyperglycemia and hyperinsulinemia in elevated insulin resistance may be related to the development of EGC.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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