Journal of Integrative Oncology
ISSN: 2329-6771

Choe and Kang, J Integr Oncol 2015, 4:4
DOI: 10.4172/2329-6771.1000153

Research Article Open Access

The Serum Carcinoembryonic Antigen is Associated with HbA1c in Korean Non-Smokers

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Abstract

Background: The carcinoembryonic antigen (CEA) is widely used as a tumor marker because of its overexpression in adenocarcinomas, particularly colorectal cancer. The aim of this study was to investigate the metabolic factors including visceral obesity that are associated with serum CEA levels in non-smokers.

Methods: This was a cross-sectional study of 1958 Koreans (1181 males, mean age 54.6 ± 8.7 years) who underwent serum CEA level and computed tomography-based visceral fat area assessments on the same day as a screening examination. The subjects were divided into 2 groups according to their median CEA level (1.20 ng/mL).

Results: The multivariable analysis revealed that CEA was associated with age (OR=1.029, 95% CI=1.017 – 1.040, P<0.001), being male (OR=1.650, 95% CI=1.210 – 2.250, P=0.002) and glycosylated hemoglobin (HbA1c) values (OR=1.386, 95% CI=1.103 – 1.742, P=0.005) but not with visceral fat area after adjusting for age, gender and other variables. Among the diabetic patients, the mean CEA level was significantly higher in the group with HbA1c values ≥ 7.0% than in those with HbA1c values<7.0% (P=0.023). After adjusting for confounding factors, the association between CEA levels and poorly controlled diabetes (HbA1c ≥ 7.0%) persisted (OR=2.331, 95% CI=1.323 – 4.108, P=0.003).

Conclusion: A serum CEA level within the normal range was related to the HbA1c level but not to visceral fat in Korean non-smokers, particularly among those with poorly controlled diabetes.

Keywords: Carcinoembryonic antigen; Diabetes mellitus; HbA1c; Metabolic syndrome; Tumor marker

Abbreviations: CEA: Carcinoembryonic Antigen; BMI: Body Mass Index; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; CRP: C-Reactive Protein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; Hba1c: Glycosylated Hemoglobin; SD: Standard Deviation; OR: Odds Ratio; CI: Confidence Interval

Introduction

Carcinoembryonic antigen (CEA) is widely used as a tumor marker because of its overexpression in adenocarcinomas, particularly colorectal cancer [1-3]. CEA levels also increase with aging and in some non-neoplastic conditions such as smoking, chronic obstructive pulmonary disease, chronic hepatitis, hypothyroidism and obesity [4-9]. Several studies have reported that CEA levels are associated with metabolic syndrome and atherosclerosis [10-13]. A recent study reported that serum CEA levels are related to abdominal visceral fat in female non-smokers [14]. However, other studies have suggested that CEA levels are significantly associated with fasting glucose or the glycosylated hemoglobin (HbA1c) level itself rather than with insulin resistance [15,16].

In Korea, CEA is generally included in the routine health check-ups of asymptomatic subjects, although CEA is not considered to be an effective marker for cancer screening. It remains unclear how CEA levels within the normal range in asymptomatic subjects should be interpreted. Additionally, the metabolic factors that are associated with the CEA level and whether CEA is related to visceral obesity in males have not been established. Therefore, we aimed to investigate the metabolic factors including visceral obesity that are associated with serum CEA levels in healthy Korean non-smokers.

Materials and Methods

Study population

We performed a retrospective, cross-sectional study. The clinical records of 22412 consecutive subjects who underwent comprehensive health evaluations that included serum CEA between January and December 2013 at the Seoul National University Hospital Healthcare System Gangnam Center were reviewed. Of these subjects, 2373 underwent abdominal fat CT assessments on the same day. We excluded 359 subjects who met one of the following exclusion criteria: current or former smoker, history of colorectal cancer or other malignancy, inflammatory bowel disease, history of chronic liver disease and abnormal liver or kidney function (AST or ALT ≥ 80 IU/L, creatinine ≥ 1.4 mg/dL). Additionally, we excluded 56 subjects with abnormal CEA data (>5.0 ng/mL) to minimize the effects of unknown cancers and other benign conditions that affect tumor marker levels such as proinflammatory conditions. Ultimately, 1958 subjects were enrolled in this study and were further analyzed. The study data included information obtained with a questionnaire, an anthropometric

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Received November 20, 2015; **Accepted** November 27, 2015; **Published** December 13, 2015

Citation: Choe EK, Kang HY (2015) The Serum Carcinoembryonic Antigen is Associated with HbA1c in Korean Non-Smokers. J Integr Oncol 4: 153. doi:10.4172/2329-6771.1000153

assessment, the laboratory data and the abdominal adipose tissue area measured by a CT scan. The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital (H1504-027-662). The need to obtain informed consent from the subjects was waived by the committee.

Measurements

The laboratory evaluation included measurements of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), fasting glucose and HbA1c. Venous blood samples were taken before 10 AM after a 12-hour overnight fast. The CEA levels were measured with immunoradiometric assay (IRMA) using a RADIM (Rome, Italy). The height and body weight of the patients were measured using a digital scale. Body mass index (BMI, kg/m^2) was calculated as the weight divided by the height squared, and waist circumference was measured at the midpoint between the lower costal margin and the iliac crest by a well-trained nurse. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg and/or the current use of antihypertensive agents. Subjects with fasting plasma glucose levels ≥ 126 mg/dL, an HbA1c ≥ 6.5% and those currently on antidiabetic treatments were defined as having diabetes mellitus (DM).

The subjects were examined with a 16-detector row CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Forchheim, Germany) in the supine position. The adipose tissue area was measured using a CT software program (Rapidia 2.8; INFINITT, Seoul, Korea) that electronically determined the adipose tissue area by setting the attenuation values for a region of interest within a range of -250 to -50 Hounsfield units as described previously [17,18].

Statistical analysis

The subjects were divided into 2 groups according to their CEA levels. The baseline characteristics were compared using the chi-squared test and Student's t-test for the categorical and continuous variables, respectively. In the subgroup analysis, the diabetic patients were divided into two groups according to their glycemic control state based on a serum HbA1c level of 7.0% as specified by current HbA1c target guidelines [19,20]. Univariate and multivariate logistic regression models were used to identify the independent associations between the risk factors and CEA levels. For each variable, the odds ratio (OR) and 95% confidence interval (CI) were calculated. The statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was established as a two-sided P value <0.05.

Results

A total of 1958 subjects (1181 males, mean age 54.6 ± 8.7 years) were analyzed in this study. The mean (standard deviation, SD) and median (interquartile range, IQR) CEA values in this study were 1.29 (0.62) and 1.20 (0.80-1.60) ng/mL, respectively. The baseline characteristics of the subjects stratified by the median CEA are compared in (Table 1). The CEA>1.20 group was older and had a greater proportion of males compared to the subjects in the CEA ≤ 1.20 group. The CEA>1.20 group had significantly greater BMI, waist circumference, visceral fat area, triglycerides, AST, ALT, creatinine, fasting glucose and HbA1c values. The CEA >1.20 group also had significantly higher prevalences of hypertension and DM than the CEA ≤ 1.20 group.

The multivariable analysis revealed that CEA was associated with age (OR=1.029, 95% CI=1.017 – 1.040, P<0.001), being male (OR=1.650, 95% CI=1.210 – 2.250, P=0.002) and HbA1c levels (OR=1.386, 95% CI=1.103 – 1.742, P=0.005) but not with visceral fat area (OR=0.999, 95% CI – 0.996 – 1.001, P=0.307) after adjusting for age, gender and other variables (Table 2). When we divided the subjects according to gender, we found no significant relationship between visceral fat and CEA levels in the males or females (P>0.05).

	Total n=1958	CEA ≤ 1.20 n=1014	CEA>1.20 n=944	P value
Age, years	54.6 ± 8.7	53.5 ± 8.3	55.7 ± 9.0	<0.001
Male gender	1181 (60.3)	561 (55.3)	620 (65.7)	<0.001
Diabetes mellitus	178 (9.1)	67 (6.6)	111 (11.8)	<0.001
Hypertension	256 (13.1)	115 (11.3)	141 (14.9)	0.018
Body mass index, kg/m^2	23.5 ± 2.8	23.3 ± 2.9	23.6 ± 2.8	0.009
Waist circumference, cm	84.9 ± 8.0	84.4 ± 8.0	85.4 ± 7.8	0.003
Visceral fat area, cm^2	115.2 ± 52.9	111.8 ± 52.6	118.8 ± 53.0	0.003
Subcutaneous fat area, cm^2	156.1 ± 58.7	159.3 ± 60.7	152.7 ± 56.3	0.028
Total cholesterol, mg/dL	197.4 ± 34.9	198.2 ± 34.7	196.6 ± 35.1	0.261
Triglycerides, mg/dL	105.1 ± 62.9	102.5 ± 62.2	108.0 ± 63.6	0.034
HDL cholesterol, mg/dL	53.7 ± 11.9	53.8 ± 11.9	53.6 ± 12.0	0.544
LDL cholesterol, mg/dL	124.9 ± 30.6	126.3 ± 31.1	123.4 ± 30.1	0.042
Fasting glucose, mg/dL	96.5 ± 17.9	94.8 ± 15.4	98.3 ± 20.2	0.001
HbA1c, %	5.66 ± 0.65	5.59 ± 0.50	5.73 ± 0.77	<0.001
CRP, mg/dL	0.14 ± 0.45	0.15 ± 0.50	0.14 ± 0.38	0.492
AST, IU/L	24.8 ± 8.3	24.4 ± 8.3	25.3 ± 8.4	0.004
ALT, IU/L	25.4 ± 13.0	24.8 ± 12.8	26.1 ± 13.2	0.009
Creatinine, mg/dL	0.84 ± 0.17	0.82 ± 0.17	0.85 ± 0.16	<0.001

The data are presented as the means ± the SD or numbers (%).
HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: hemoglobin A1c; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SD: standard deviation.

Table 1: Baseline characteristics according to CEA concentration.

	Univariate analysis			Multivariable analysis		
Factor	OR	95% CI	P value	OR	95% CI	P value
Age, years	1.030	1.019-1.041	<0.001	1.029	1.017-1.040	
Male	1.545	1.287-1.855	<0.001	1.650	1.210-2.250	0.002
Hypertension	1.373	1.054-1.787	0.018	1.021	0.769-1.356	0.883
Body mass index ≥ 25 kg/m^2	1.292	1.061-1.574	0.011	1.230	0.943-1.604	0.128
Waist circumference, cm	1.017	1.005-1.028	0.004	0.518	0.974-1.013	0.993
Visceral fat area, cm^2	1.003	1.001-1.004	0.004	0.999	0.996-1.001	0.307
Fasting glucose, mg/dL	1.011	1.006-1.017	<0.001	0.999	0.992-1.007	0.892
HbA1c, %	1.456	1.240-1.711	<0.001	1.386	1.103-1.742	0.005
AST, IU/L	1.013	1.002-1.024	0.020	1.005	0.987-1.023	0.571
ALT, IU/L	1.007	1.001-1.014	0.034	0.999	0.987-1.011	0.895
Creatinine, mg/dL	2.585	1.515-4.411	<0.001	1.094	0.456-2.424	0.907

The multivariable model was adjusted for patient age, gender, hypertension, body mass index, waist circumference, visceral fat area, fasting glucose, HbA1c, AST, ALT and creatinine.
OR: odds ratio; CI: confidence interval; HbA1c: hemoglobin A1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 2: Univariate and multivariable odds ratios of various clinical variables for CEA>1.20 ng/mL.

To evaluate the association between CEA levels and HbA1c, we performed a subgroup analysis in the patients with diabetes. The patients with diabetes were divided into two groups according to their glycemic control state based on an HbA1c level of 7.0% as specified in the current HbA1c target guidelines (Table 3). There were no significant differences between the groups in age, gender or the majority of the anthropometric assessments and laboratory tests with the exceptions of fasting glucose and HbA1c and CEA levels. The mean CEA level was 1.37 ± 0.54 ng/mL in the group with lower HbA1c values (HbA1c<7.0%) and 1.65 ± 0.85 ng/mL in the group with higher HbA1c values (HbA1c ≥ 7.0%). The mean CEA level was significantly higher in the group with higher HbA1c values (P=0.023). The results of the univariate and multivariable analyses of the CEA level according to glycemic control state are illustrated in (Table 4). After adjusting for age, gender and BMI in the multivariate analysis, the association between the CEA level and poorly controlled DM (HbA1c ≥ 7.0%) persisted (OR=2.331, 95% CI=1.323 – 4.108, P=0.003).

	Diabetes n=178	HbA1c<7.0 % n=118	HbA1c ≥ 7.0 % n=60	P value
Age, years	58.6 ± 9.0	58.8 ± 8.7	58.2 ± 9.8	0.687
Male gender	120 (67.4)	82 (69.5)	38 (63.3)	0.407
Hypertension	56 (31.5)	37 (31.4)	19 (31.7)	0.966
Body mass index, kg/m^2	24.6 ± 3.1	24.7 ± 2.9	24.5 ± 3.4	0.686
Waist circumference, cm	88.6 ± 8.2	88.9 ± 7.7	88.1 ± 9.1	0.521
Visceral fat area, cm^2	140.5 ± 55.8	141.7 ± 55.1	138.1 ± 57.5	0.688
Subcutaneous fat area, cm^2	162.0 ± 69.3	159.2 ± 63.5	167.3 ± 79.8	0.462
Total cholesterol, mg/dL	184.1 ± 42.1	181.3 ± 41.0	189.6 ± 44.1	0.215
Triglycerides, mg/dL	131.1 ± 73.7	124.1 ± 60.9	144.9 ± 93.2	0.120
HDL cholesterol, mg/dL	51.2 ± 12.7	51.5 ± 13.5	50.7 ± 11.2	0.678
LDL cholesterol, mg/dL	113.6 ± 35.1	111.5 ± 33.6	117.8 ± 37.7	0.264
Fasting glucose, mg/dL	134.3 ± 29.4	122.8 ± 19.2	156.8 ± 32.9	<0.001
HbA1c, %	7.03 ± 1.28	6.38 ± 0.38	8.31 ± 1.47	<0.001
CRP, mg/dL	0.25 ± 0.69	0.21 ± 0.59	0.32 ± 0.85	0.306
AST, IU/L	27.2 ± 10.6	27.0 ± 10.3	27.7 ± 11.0	0.651
ALT, IU/L	30.4 ± 15.0	29.9 ± 14.4	31.4 ± 16.4	0.546
Creatinine, mg/dL	0.82 ± 0.17	0.83 ± 0.18	0.79 ± 0.17	0.144
CEA, ng/mL	1.46 ± 0.68	1.37 ± 0.54	1.65 ± 0.85	0.023

The data are presented as the means ± SD or numbers (%).
HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: hemoglobin A1c; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SD: standard deviation.

Table 3: Baseline characteristics of the diabetic patients according to glycemic control state.

Discussion

In the present study, CEA was significantly associated with HbA1c levels in Korean non-smokers. When the diabetic patients were divided according to glycemic control state, CEA was found to be associated with HbA1c only in the higher HbA1c group after adjusting for confounding factors. The results of our study correspond with those of a previous study that HbA1c is positively associated with serum CEA levels [15]. However, unlike the previous study, we did not observe a relationship between visceral obesity and CEA levels in either females or males [14]. Visceral adipose tissue is known to be a metabolically active organ that secretes cytokines, growth factors and adhesion molecules that promote the development of obesity-related pathologic conditions [21]. A previous study by Lee et al. suggested that serum CEA levels are correlated with the abdominal visceral fat area in female non-smokers and that CEA may be a mediator that links metabolic disturbances and tumorigenesis in visceral obesity [14]. However, the study of Lee et al. suffered the limitations of a small sample size and the enrollment of only females.

Based on our results, it might be possible to use the serum CEA level and the HbA1c value in combination. There are many studies that have reported significant relationships between DM and colorectal cancer [22-24]. Therefore, assessing CEA levels following sudden elevations in HbA1c levels in well-controlled diabetic patients could be considered for the purpose of excluding colorectal neoplasm. Moreover, when serum CEA levels are elevated in a cancer screening without evidence of malignancy, diabetes could be suspected.

The mechanisms linking the CEA level and HbA1c are not clear. Previous studies of the association of CEA levels with metabolic syndrome have suggested several mechanisms that generally emphasize the relationship between CEA levels and inflammation. CEA may stimulate macrophages or monocytes via binding to the CEA receptor, which results in the production of inflammatory cytokines and adipokines [10,25]. Inflammation is now recognized as having a central role in the pathogenesis of insulin resistance and metabolic syndrome [26]. Additionally, CEA levels are elevated in chronic inflammatory diseases such as chronic viral hepatitis, inflammatory bowel disease and collagen disease [5,6,27]. Furthermore, a direct association of CEA with visceral adiposity in the absence of any mediator has been hypothesized [14]. However, our study did not observe significant relationships of the CEA level with visceral fat or metabolic components including waist circumference, triglycerides, HDL cholesterol or fasting glucose in the multivariate analysis. A previous study by No et al. also suggested that serum CEA levels are influenced by the HbA1c level itself rather than by insulin resistance [15]. Additionally, several studies have reported that serum CEA levels and carbohydrate antigen 19-9 (CA 19-9), a tumor marker in pancreatic cancer, could be influenced by high glucose levels and HbA1c in diabetic patients [12,28-30]. These results may be a result of the following similar components such as glucose, glycoprotein, HbA1c and the lipids of CEA and CA 19-9 [31,32]. Further studies are required to explain this topic.

			Univariate analysis			Multivariable analysis		
	CEA ≤ 1.20	CEA>1.20	OR	95% CI	P value	OR	95% CI	P value
Control (reference)	947 (53.2)	833 (46.8)	1.00			1.00		
Well-controlled diabetes (HbA1c<7.0%)	49 (41.5)	69 (58.5)	1.601	1.097-2.336	0.015	1.337	0.909-1.968	0.140
Poorly controlled diabetes (HbA1c ≥ 7.0%)	18 (30.0)	42 (70.0)	2.653	1.515-4.644	0.001	2.331	1.323-4.108	0.003

The multivariable model was adjusted for patient age, gender and body mass index.
OR: odds ratio; CI: confidence interval.

Table 4: Univariate and multivariable analyses of the CEA level and glycemic control.

This study has several limitations. First, the subjects of this study were self-recruited for routine medical check-ups, which might have caused selection bias; thus, our results may not reflect the general population. Second, this was a cross-sectional study. Therefore, we were unable to examine the causal or temporal relationships between CEA levels and HbA1c. Third, the serum CEA level is known to be influenced by several other non-neoplastic conditions, such as hypothyroidism and chronic obstructive pulmonary disease, which we did not consider as exclusion criteria or confounding factors. Fourth, we could not examine the relationships between HbA1c and CEA beyond an upper limit because we included only patients with CEA levels within the normal range in terms of the effects of unknown malignancies or other inflammatory conditions. However, the strength of this study was the inclusion of a large number of asymptomatic non-smokers. Moreover, important laboratory evaluations and abdominal fat CT data were included and allowed for the consideration of various confounding factors because we enrolled subjects who underwent comprehensive health check-ups. Previous studies have been limited by small sample sizes and the lack of visceral fat data from males.

In conclusion, the present study revealed that within the normal range, the serum CEA level is significantly associated with HbA1c but not with visceral fat in non-smokers. Furthermore, the serum CEA levels were relatively high in the diabetic patients with poor glycemic control states. These findings reinforce the close relationship between CEA levels and HbA1c in diabetic patients and also suggest that serum CEA levels might reflect the glycemic control states of diabetic patients. However, further studies are required to explain the underlying mechanisms connecting HbA1c to CEA levels.

Authors' Contributions

HYK and EKC designed and performed the research. EKC and HYK analyzed the data and wrote the paper. All of the authors have approved the final version.

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