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## The Role of Metabolic Syndrome and Related Clinical Variables in Determining CEA Levels

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**A** – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

### Abstract

**Objectives.** The aim of the study was to investigate how metabolic syndrome (MetS) and related clinical variables correlate with high levels of carcinoembryonic antigen (CEA).

**Material and Methods.** Variables related to MetS as well as the serum CEA levels of 366 subjects were assayed. Logistic regression analyses were used to determine the associations between various clinical variables and high CEA levels, which were defined as values greater than the median (i.e., 1.4 ng/mL).

**Results.** MetS, as an entity, and diabetes were more prevalent in subjects with high CEA levels (for MetS: 64.2% in subjects with CEA  $\geq$  1.4 vs. 51.1% in subjects with CEA  $<$  1.4 ng/mL,  $p < 0.05$ ; for diabetes: 72.6% vs. 59.1% respectively,  $p < 0.05$ ). Waist circumference, triglycerides, fasting plasma glucose (FPG), homeostasis-model assessment of insulin resistance index (HOMA-IR), and HbA<sub>1c</sub> as well as systolic and diastolic blood pressures were directly associated with CEA levels, after adjusting for age and sex ( $p < 0.05$ ). Subjects with a greater number of MetS components tended to have high CEA levels. Multivariate regression analysis revealed that the association of waist circumference and FPG with CEA is independent of other MetS components, age and sex.

**Conclusions.** MetS and related clinical variables contribute to CEA values. Thus, the reference interval of CEA may differ according to the clinical status of the subjects (**Adv Clin Exp Med 2014, 23, 6, 907–912**).

**Key words:** CEA, metabolic syndrome, obesity, insulin resistance.

Carcinoembryonic antigen (CEA), a glycoprotein with a molecular weight of approximately 200 kDa, is widely used as a tumor marker for adenocarcinomas, particularly colorectal cancer [1, 2]. It is also expressed in a number of normal tissues including the tongue, esophagus, stomach, colon, cervix and prostate [3]. Besides cancer, CEA is related to several non-malignant conditions such as renal and hepatic failure, pulmonary disease, chronic inflammatory disease and aging [4–8].

Metabolic syndrome (MetS) refers to a clustering of various cardiovascular and diabetes mellitus risk factors including central obesity, dyslipidemia, insulin resistance and hypertension [9]. MetS is highly prevalent and is an increasingly common medical condition globally [10, 11]. The

underlying pathophysiological pathways involved in the clustering of MetS components are not fully understood [12]. However, insulin resistance has been regarded to play an important role in the pathogenesis of MetS [13]. In addition to cardiovascular diseases and diabetes, subjects with MetS are also prone to certain types of malignancies (e.g. colorectal cancer) [14–16]. Furthermore, a review of previous studies shows that the odds of having MetS increases with age, which *per se* augments the risk of some cancers [17, 18].

According to the aforementioned findings, both CEA and MetS are related to certain types of malignant and non-malignant conditions. The aim of the current study was to evaluate the roles of different clinical variables in determining CEA levels.

This study is the first to report on the correlations between high CEA levels and wide variety of MetS-related variables.

## Material and Methods

### Participants

A total of 366 individuals (aged 30 to 70 years) who visited an outpatient clinic of Vali-Asr hospital (a Tehran University-affiliated medical center) from June 2008 to March 2012 were enrolled in the current study. The participants enrolled were both individuals seeking health examinations and those who accompanied patients. Most subjects asking for health examinations were short-term diabetic patients, and the reason for referring them to the clinic was to monitor blood glucose levels. Individuals with a prior diagnosis of any cancer, hepatic, renal, thyroid or adrenal problems, as well as those taking insulin, antihypertensive medications or lipid modifying agents were excluded from the study. Individuals with a smoking habit were also excluded. Diabetic participants were receiving metformin, glibenclamide or both concurrently to control their glycemic status. Oral informed consent was obtained from all participants before the study commenced. The study was performed in line with the Helsinki declaration and the recommendations of the local ethics review committee of Tehran University of Medical Sciences.

### Assessments

Waist circumference was measured to the nearest 0.1 cm at the end of a normal expiration in standing position at the midpoint between the iliac crest and the rib cage. After resting for at least 5 min, systolic and diastolic blood pressures were measured twice, separated by an interval of at least 5 min. The average of these 2 measurements was used in the analyses. Venous blood samples were collected after a 12-h overnight fast. Fasting plasma glucose (FPG) was measured by a glucose oxidase test (intra- and inter-assay coefficients of variation less than 2.1 and 2.6, respectively). Triglycerides, high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) were assayed by enzymatic techniques (Parsazmun, Karaj, Iran), and apolipoproteins A-I and B were determined by the immunoturbidimetric method (Roche, Basel, Switzerland). For apolipoprotein A-I the intra- and inter-assay coefficients of variation were lower than 1.0 and 2.4, and for apolipoprotein B these values were lower than 1.2 and 3.2, respectively. Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was assessed using the high performance liquid chromatography method. Insulin was

determined by radioimmunoassay, using an antibody with no cross-reactivity for pro-insulin and C-peptide (Immunotech, Prague, Czech Republic). The intra- and inter-assay coefficients of variation were lower than 4.3 and 3.4, respectively. C-peptide was measured by radioimmunoassay (Immunotech, Prague, Czech Republic). CEA was measured using the electrochemiluminescent method (Roche, Basel, Switzerland). Finally, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were also assessed, using commercial available kits.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (U/L)  $\times$  fasting plasma glucose (mg/dL)/405 [19]. MetS was defined in accordance with the modified International Diabetes Federation (IDF) criteria. According to these criteria, abdominal obesity (i.e. waist circumference  $\geq$  90 cm in both men and women) must be present, along with any 2 or more of the following conditions: elevated blood pressure (systolic blood pressure  $\geq$  130 mm Hg and/or diastolic blood pressure  $\geq$  85 mm Hg) or treatment for previously diagnosed hypertension, low HDL-C ( $<$  40 mg/dL and  $<$  50 mg/dL in men and women, respectively) or on HDL-C therapy, triglycerides  $\geq$  150 mg/dL or on triglyceride therapy and fasting plasma glucose  $\geq$  100 mg/dL (or diabetes) [9].

### Statistical Analysis

The subjects were divided into 2 groups according to their CEA levels. Continuous and categorical variables were compared between these 2 groups, using Student's *T*-test and the  $\chi^2$  test, respectively. A logistic regression analysis was run separately for each variable, with age and sex as co-variables. In all the regression analyses, the CEA was treated as the dependent variable in the dichotomous form of lower/higher than the median. Additionally, considering subjects with no MetS component and those with one MetS component together as the reference group, the odds ratios of having 2, 3, or  $>$  3 MetS components was also calculated. Then, a multivariate regression model was designed to evaluate the association of various clinical variables with CEA. The data were analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, USA), and the *p* value  $<$  0.05 was considered statistically significant.

## Results

The mean (standard deviation, SD) and median (interquartile range, IQR) of CEA in the studied sample were equal to 1.69 (1.20) ng/mL and 1.40 (0.90–2.20) ng/mL, respectively. Table 1 shows the

principal characteristics of the subjects stratified by CEA at the median. Subjects with CEA levels higher than the median also had higher waist circumference, triglycerides, FPG, systolic and diastolic blood pressures ( $p < 0.05$ ). Thus, among MetS components, only HDL-C was not statistically different between subjects with high and low levels of CEA. Subjects with CEA levels greater than the median, were older and were comprised of a higher proportion of men ( $p < 0.05$ ). Further, the frequencies of diabetes and MetS were higher in subjects with CEA  $\geq 1.4$  ng/mL ( $p < 0.05$ ).

**Table 1.** Principal characteristics of the study population

	CEA < 1.4 ng/mL (n = 176)	CEA $\geq 1.4$ ng/mL (n = 190)
Male, number (%)	54 (30.7)	82 (43.2)*
Age, years	51.3 $\pm$ 10.3	54.4 $\pm$ 9.5**
Waist circumference, cm	92.9 $\pm$ 12.5	97.6 $\pm$ 11.5***
Triglycerides, mg/dL	158.1 $\pm$ 81.7	185.9 $\pm$ 110.1**
HDL-C, mg/dL	49.3 $\pm$ 12.4	47.7 $\pm$ 12.8
LDL-C, mg/dL	111.6 $\pm$ 33.8	106.4 $\pm$ 36.1
Apolipoprotein A-I, mg/dL	140.3 $\pm$ 30.0	140.6 $\pm$ 27.5
Apolipoprotein B, mg/dL	90.1 $\pm$ 26.3	91.4 $\pm$ 26.5
FPG, mg/dl	123.0 $\pm$ 34.8	140.4 $\pm$ 52.4***
Fasting plasma insulin, U/L	9.27 $\pm$ 4.99	9.95 $\pm$ 8.83
C-peptide, ng/mL	2.46 $\pm$ 1.03	2.42 $\pm$ 1.26
HOMA-IR, unites	2.82 $\pm$ 1.69	3.30 $\pm$ 2.64*
Hb A <sub>1c</sub> , %	6.51 $\pm$ 1.48	6.94 $\pm$ 1.59**
Systolic blood pressure, mm Hg	121.8 $\pm$ 14.1	125.9 $\pm$ 15.8**
Diastolic blood pressure, mm Hg	79.3 $\pm$ 6.96	80.8 $\pm$ 7.69*
ALT, U/l	30.2 $\pm$ 19.2	27.8 $\pm$ 16.7
AST, U/l	21.7 $\pm$ 9.8	21.3 $\pm$ 9.5
ALP, U/l	136.8 $\pm$ 50.4	127.1 $\pm$ 45.1
Diabetes, Number (%)	104 (59.1)	138 (72.6)**
MetS, Number (%)	90 (51.1)	122 (64.2)*

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Data are presented as mean  $\pm$  standard deviation (SD) unless otherwise stated.

Table 2 shows the odds ratios of various variables for CEA  $\geq 1.4$  ng/mL after adjusting for age and sex. HDL-C was determined to be the only MetS components which was not associated with high CEA levels. Among insulin resistance measures, FPG, HOMA-IR and HbA<sub>1c</sub> were associated with CEA ( $p < 0.05$ ). In addition, subjects with either 4 or all 5 components of MetS were more likely to have high CEA levels than those who had one or no MetS component ( $p < 0.05$ ).

The traditional components of MetS that were initially associated with CEA (i.e., waist circumference, triglycerides, FPG and systolic blood pressure), along with age and sex, were entered to a multiple regression analysis model (Table 3). It was found that triglycerides and systolic blood pressure cannot be regarded as independent determinants of CEA. In contrast, the associations of

**Table 2.** Age- and sex-adjusted odds ratios of various clinical variables for CEA  $\geq 1.4$  ng/mL

	Odds ratio	95% confidence interval
Waist circumference, cm	1.035***	1.016, 1.055
Triglycerides, mg/dL	1.003**	1.001, 1.006
HDL-C, mg/dL	0.988	0.972, 1.005
LDL-C, mg/dL	0.997	0.991, 1.003
Apolipoprotein A-I, mg/dL	1.001	0.994, 1.009
Apolipoprotein B, mg/dL	1.003	0.995, 1.011
FPG, mg/dl	1.025*	1.003, 1.047
Fasting plasma insulin, U/L	1.024	0.991, 1.057
C-peptide, ng/mL	1.007	0.768, 1.321
HOMA-IR, unites	1.127*	1.016, 1.250
HbA <sub>1c</sub> , %	1.161*	1.006, 1.340
Systolic blood pressure, mm Hg	1.019*	1.004, 1.033
Diastolic blood pressure, mm Hg	1.029*	1.000, 1.059
MetS components		
Any 2 components <sup>1</sup>	1.531	0.816, 2.872
Any 3 components <sup>1</sup>	1.694	0.905, 3.171
Any 4 or more components <sup>1</sup>	3.765*	1.050, 7.279

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Odds ratios are estimated for one-unit increases in each of the variables unless otherwise stated.

<sup>1</sup> Odds ratios are determined for existence of a condition against those who have either zero or one MetS component.

**Table 3.** The multivariate adjusted odds ratios of MetS components for CEA  $\geq$  1.4 ng/mL

	Odds ratio	95% confidence interval
Waist circumference, cm	1.025*	1.005, 1.045
Triglycerides, mg/dL	1.002	1.000, 1.004
FPG, mg/dL	1.006*	1.001, 1.012
Systolic blood pressure, mm Hg	1.008	0.993, 1.024

\*  $p < 0.05$ .

The odds ratios are reported for a model designed to include waist circumference, triglycerides, FPG, systolic blood pressure as well as age and sex. Odds ratios are estimated for one-unit increases in each of the variables.

waist circumference and FPG with high CEA levels were independent of age, sex and other MetS components ( $p < 0.05$ ).

## Discussion

The current study is the first to evaluate the association of a large number of clinical variables with CEA. Among MetS components, HDL-C was the only variable that was not associated with CEA. Although triglycerides and systolic blood pressure were initially identified as determinants of high CEA levels, they did not remain in the model after adjusting for waist circumference and FPG. In contrast, waist circumference and FPG correlated with high CEA levels independently of age, sex, and other MetS components.

The association of MetS and its components with colorectal cancer has been the subject of several studies [14, 20–22]. Studies reporting the association between CEA and MetS and its components are limited. In the current study, the initial regression models showed significant associations between CEA and triglycerides and systolic blood pressure; these findings are supported by prior studies [26, 27]. However, when triglycerides and systolic blood pressure were entered into multivariate regression analyses along with other MetS components, they dropped out of the model. This suggests that the association initially observed between these 2 variables and CEA was a consequence of their correlation with other MetS components. By contrast, the association of waist circumference and FPG with CEA was identified to be independent of other MetS components, age and sex. In a general agreement with the findings of the current study, Ishizaka et al. reported a direct association between CEA and fasting glucose and HbA<sub>1c</sub> [28]. The

current study shows that besides FPG and HbA<sub>1c</sub>, HOMA-IR, a widely used insulin resistance measure, is also associated with CEA.

Since MetS and its components are considered atherogenic factors, it may be plausible to suggest that subjects with high CEA levels are prone to vascular events. In this regard, some earlier studies have suggested CEA as an independent determinant of acute coronary events and carotid atherosclerosis [28, 29].

Although no prior study has reported the pathophysiological pathways that underlie the association of MetS and CEA, there is some speculation in the literature regarding the carcinogenic role of MetS. It has been shown that subjects with MetS tend to have hyperinsulinemia and high levels of insulin resistance measures [9, 12]. Considering the fact that insulin and some of its precursors (i.e. pro- and pre-insulin) have a partial affinity to receptors of the tumor growth factor, an association between diabetes mellitus, insulin, hyperinsulinemia, and carcinogenesis appears plausible [30]. Further, insulin resistant subjects have elevated basal lipolysis, and consequently increased intracellular concentrations of free fatty acids, which may impair growth control in non-adipose cells. This phenomenon is referred to as lipotoxicity [31, 32]. Insulin resistance may also lead to an imbalance in the level of sex steroids and subsequently to the development of malignant cells [33–35]. The role of obesity as a cause of cancer has been also studied. For instance, obesity is related to higher levels of some inflammatory markers (e.g., TNF- $\alpha$  and IL-6), which can contribute to malignant diseases [32, 36–38]. To evaluate the exact role of obesity in this, CEA expression in fat cells may need to be assessed. Considering the role of CEA as a tumor marker, it is reasonable to say that the aforementioned pathways may be at least partially responsible for the observed association between various MetS-related clinical variables and CEA.

A review of previous studies shows that there are some minor variations in the reference intervals of CEA between different ethnic groups [39–41]. Additionally, Qin et al have suggested distinct reference intervals for smoking and non-smoking populations [42]. CEA is also related to gender, age and menopause status [39, 40, 43]. In the current study, the authors showed for the first time that besides the aforementioned factors, the insulin resistance status of subjects may also alter CEA levels. Thus, while interpreting CEA levels, in addition to the patients' age, sex and smoking habits, clinicians should also consider their insulin resistance status.

There have been few studies reporting the association of CEA with a wide variety of anthropometric and metabolic measures. Using multiple regression models, the current study evaluated

independent associations between various clinical variables and CEA concentration for the first time. It is worth noting that although the odds ratios were significant from a statistical point of view, the magnitude of the odds ratios was not remarkable. One possible reason is that the odds ratios are reported for each unit of increase in the variables. Conducting the analyses for higher magnitudes of change in the value of variables (e.g. every ten units) would result in higher odds ratios. Moreover, because cross-sectional data was used, the current study could not determine the direction of causality in the relationship between MetS components and CEA. Furthermore, when interpreting the results, it is important to be cautious about the variation coefficients of the laboratory measurements. Further studies are needed to

determine which tissues/organs are mostly responsible for the higher values of CEA in the subjects with MetS components.

The current study suggests that CEA is influenced by a cluster of anthropometric and metabolic variables. Among MetS components, only HDL-C has no association with CEA. By contrast, waist circumference and FPG correlate with high CEA levels even after adjusting for other MetS components, age, and sex. Thus, the reference interval of CEA may be different according to the insulin resistance status and MetS status of the subjects. This study, in conjunction with other studies, can help clinicians to individualize the value of CEA for use in follow-up programs. Further studies are also needed to elucidate the underlying pathophysiological pathways linking MetS to high CEA levels.

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