

Original Article

Association between serum carcinoembryonic antigen level and oxidative stress parameters among diabetic females

Marghoob Hasan, Abdelmarouf Mohieldein

Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University P. O. Box 6699 Buraidah 51452, Saudi Arabia

Received December 29, 2014; Accepted March 26, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: In this study we intended to determine serum level of the carcinoembryonic antigen (CEA) and to find out the correlation with oxidative stress parameters among diabetic female in comparison to control subjects. Methods: A total of 120 Saudi (type 2 diabetic "T2DM", n = 60 and healthy non-diabetic, n = 60) nonsmokers females were enrolled in this study. Body mass index (BMI) was estimated using weight and height; CEA, superoxide dismutase (SOD), 8-hydroxy-deoxyguanosine (8-OHDG), malondialdehyde (MDA) were performed using enzyme-linked immunosorbent assay (ELISA) kits. Blood glucose was estimated by GOD/POD method and, glycated haemoglobin (HbA1c) by immunoturbidimetric method. Results: The student's t-test showed significant differences between the diabetics and controls in CEA, blood glucose, age, oxidative stress markers. Moreover, Pearson's correlation coefficient (r) indicated significant correlations between CEA and age, BMI, blood glucose, HbA1c, and MDA. No significant correlation was found between CEA and 8-OHdG, SOD. Conclusions: In this study we confirmed that CEA influence with components of type 2 diabetes and glycemic control. We found correlation between Lipid peroxidation and CEA among diabetic female in comparison to control subjects.

Keywords: Diabetes mellitus, serum carcinoembryonic antigen, oxidative stress, cancer marker, malondialdehyde

Introduction

Type 2 diabetes mellitus (T2DM) is a complex heterogeneous group of metabolic disorders characterized by hyperglycemia and impaired insulin action and/or insulin secretion [1]. Recently one study has indicated that the prevalence of diabetes among Saudi females is around 27.6% in all the participants. In Saudi population it represents a major clinical and public health problem [2]. Epidemiologic evidence suggests that cancer incidence is associated with diabetes as well as certain diabetes risk factors and diabetes treatments [3]. More recently, meta-analytic study concluded that almost 1.2 fold of risk of breast cancer among diabetic mellitus type 2 predominantly [4].

Carcinoembryonic antigen (CEA) is a 180 kDa oncofetal glycoprotein and a well-known soluble tumor marker [5]. Although its presence in normal tissues is mainly limited to the large intestine, it is over expressed in most gastroin-

testinal malignancies, lung cancer, in almost 50% of breast cancer and thyroid cancer [6, 7]. Studies indicated that in several non-neoplastic conditions like acute and chronic inflammations, benign tumors, renal or hepatic insufficiency serum levels of CEA is elevated [8]. A recent study has indicated that CEA values are increased in metabolic syndrome [9]; an increase which is dose- and duration-dependent in Japanese men. Moreover, the increase in serum CEA was found to be associated with an increased prevalence of carotid plaque independent of blood pressure, fasting glucose, serum lipids, and inflammatory markers [10]. Insulin resistance is associated with the increase of CEA. Second, visceral adiposity is positively correlated with clinical manifestations associated with insulin resistance, including type 2 diabetes and dyslipidemia [11].

Oxidative stress, through the production of reactive oxygen species (ROS), has been proposed as the root cause underlying the devel-

CEA and oxidative stress parameters among diabetic females

Table 1. Basic demographic and clinical characteristics of type 2 diabetes compared to non-diabetic control subjects

Variable	type 2 diabetes (T2DM) n = 60	Controls (non-diabetic) n = 60	*p-value
Age (yr)	56.54 ± 9.5	45.66 ± 11.3	.000*
Weight (kg)	75.97 ± 13.3	72.59 ± 15.4	.253
Height (cm)	160.9 ± 5.5	159.7 ± 14.6	.572
BMI (kg/m ²)	31.92 ± 5.8	31.39 ± 8.1	.699
Blood Glucose (mg/dl)	225.01 ± 80.4	82.64 ± 24.1	.000*
HbA _{1c} (%)	9.51 ± 2.3	4.97 ± 1.6	.000*
Duration of DM (years)	9.53 ± 6.2	—
CEA	4.36 ± 2.4	1.76 ± 1.4	0.011*
8-OHdG (ng/mL)	1.39 ± 1.2	0.38 ± 0.2	.000*
MDA (μmol/L)	2.94 ± 0.55	2.65 ± 0.57	0.023*
SOD (U/ml)	198.80 ± 39.9	221.54 ± 37.3	0.015*

*P value less than 0.05 was considered statistically significant.

Table 2. Correlation between Carcinoembryonic antigen (CEA) and age, BMI, blood glucose, glycated hemoglobin in all participants

	CEA
Age	r = 0.384* P = .036
BMI	r = 0.415* P = 0.025
Glucose	r = .634* P = .027
A1c	r = .507** P = .006

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

opment of insulin resistance, β-cell dysfunction, impaired glucose tolerance and T2DM [12]. In our literature search we do not found any study conducted in diabetic females to assess the levels of CEA and association of oxidative stress markers. Hence, in this study we intended to estimate the CEA level among diabetic females, in a situation with increased oxidative stress and to find out the correlation of oxidative stress parameters with CEA.

Materials and methods

Study design

This is a case-control study.

Study population

Sixty adult female Saudi with type 2 diabetes mellitus (age 15-60 years) recruited from

Diabetes and Endocrinology Centre, to participate in this study. Diabetes was defined as a fasting serum glucose ≥ 7.0 mmol/L (126 mg/dL), the use of anti-diabetic agents, or both. All patients were non smokers and have no history of any type of cancer.

The non-diabetic control group included 60 age and sex-matched healthy individuals. The inclusion criteria for the control subjects were neither have been diagnosed by a physician as having diabetes or use hypoglycemic medication nor be hypertensive or have any known medical condition. Controls included with this study were non-smoker females with no history of any type of cancer.

Blood sampling & measurement of body mass index (BMI)

For blood sampling, BMI, glucose, HbA_{1c}, we followed the same protocol for sample collection and processing, already reported elsewhere [13].

Laboratory analysis

CEA (carcinoembryonic antigen), superoxide dismutase (SOD), 8-hydroxy-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) were performed using ELISA kits from EIAab WUHAN EIAAB SCIENCES CO. LTD CHINA.

Statistical analysis

Results are expressed as mean ± SD. The Student's t-test was performed to compare the parameters between non-diabetic and T2DM patients. Correlation between parameters was determined by Pearson's correlation coefficient (r). A P value less than 0.05 was considered statistically significant.

Results

Characteristics of participants

Compared to controls, type 2 diabetics showed significantly increased age, blood glucose, and glycated hemoglobin. However, all participants in both groups were obese with body mass index around 31 Kg/m².

Table 3. Correlation between Carcinoembryonic antigen (CEA) and parameters of oxidative stress markers (8OHdG, MDA, SOD) in all participants

	CEA
8-OHdG	$r = 0.256$ $P = 0.172$
MDA	$r = 0.454^*$ $P = 0.020$
SOD	$r = -0.136$ $P = 0.491$

Correlation is significant at the 0.05 level (2-tailed). None significant correlation was found between Carcinoembryonic antigen (CEA) and parameters of oxidative stress (8-OHdG, SOD) except between CEA and MDA ($r = .454^$, $P = 0.020$).

Levels of CEA and oxidative stress markers

Type 2 diabetic patients characterized by significantly high levels of CEA, 8-OHdG, MDA but low SOD when compared to controls. Data presented in (Table 1).

Correlation between CEA and selected parameters

Pearson correlation test showed significant positive correlation between carcinoembryonic antigen (CEA) and age ($P = 0.036$, $r = .0384$), BMI ($P = 0.025$, $r = 0.415$), blood glucose ($P = 0.027$, $r = 0.634$), glycated hemoglobin ($P = 0.006$, $r = 0.507$) in all participants (Table 2). However, when CEA was compared with oxidative stress markers (8OHdG, MDA, SOD) in all participants; no significant correlation was found between CEA and parameters of oxidative stress (8-OHdG, SOD) except between CEA and MDA ($r = .454^*$, $P = .020$) (Table 3).

Discussion

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface glycoprotein [14]. CEA is one of the most widely used tumor markers worldwide. It is over expressed in adenocarcinomas in the colon and other organs including the pancreas, lung, prostate, urinary bladder, ovary and breast [15]. However, several non-malignant conditions, including acute and chronic inflammation and other inflammatory-related conditions such as aging and smoking are characterized by increased CEA concentrations [16]. In our study, we found that there is a

significant difference in the level of CEA between the type 2 diabetes compared to non-diabetic control subjects. Recently, a study about elevated serum CEA level and metabolic syndrome (MS) in female Korean non-smokers was reported [17]. MS confers a greater risk of type 2 diabetes [18]. Pei-Chi Chen et al [19] reported a case of diabetic male with elevated CEA level. Also, Jeep-Yon Lee et al [20] found statistically significant levels of serum CEA level in around 8% diabetic vs. non diabetic Korean female's subjects among all participants. In another study, it is reported elevated level of CEA in pancreatic cancer-associated diabetes [21].

Our results are in agreement with previous studies [16, 17] that CEA level show a positive correlation with and age, BMI, blood glucose, glycated hemoglobin in all participants. Moreover it is very much in agreement with Ure et al [22] about the glycemic control influences' on CEA values.

Oxidative stress plays a pivotal role in the development of diabetes complications [23]. Oxidative stress may be one pathway whereby obesity, insulin resistance, and the metabolic syndrome lead to T2DM in humans [24]. In this study we have found the level of oxidative stress markers among diabetic subjects as increased 8-hydroxy-deoxyguanosine (8-OHDG) [25], increased malondialdehyde (MDA) [26], but decreased superoxide dismutase (SOD) [27].

Our findings show that CEA value was positively correlated with the lipid peroxidation marker malondialdehyde (MDA). But no correlation was found with SOD, 8-OHDG, earlier studies has reported increased levels of CEA along with lipid peroxidation [22, 28]. It evident from the other studies that malondialdehyde is an endogenous genotoxic product of enzymatic and oxygen radical-induced lipid peroxidation and found to induce mutations [29]. MDA, the end product of lipid peroxidation, owing to its high cytotoxicity has been suggested to act as a tumor promoter and a co-carcinogenic agent. Previous reports states that abnormal glucose metabolism was associated with a statistically significantly increased risk of cancer overall in women at many sites [30]. In addition, glucose itself may support carcinogenic processes through the generation of free radicals, and the

induction of oxidative damage to both DNA and to the enzymes involved in the repair and processing of DNA. Insulin has recently obtained attention as metabolic factor related to risk of breast cancer and colon cancer [31]. Insulin has a mitogenic effect on mammary epithelium cells and it has been observed that the insulin receptor is over expressed in both human breast cancer and human breast tissues [32].

In addition, inflammation has been implicated as an important aetiological factor in the development of both insulin resistance and T2DM [33]. There is an association between elevated levels of circulating acute phase inflammatory markers and indices of insulin resistance and the development of T2DM [34]. In the past three decades, both cardiovascular disease (CVD) and diabetes, in particular obesity-induced T2D, have been recognized as inflammatory diseases [35]. The systemic low-grade inflammatory response that is often observed in obesity detrimentally affects both insulin signaling and b-cell function and may thus contribute to the development of T2DM [36].

Previous studies have reported that elevated CEA level is related with metabolic syndrome and atherosclerosis as inflammatory deriving biological properties [20]. Adhesion molecule (ICAM-1 and VCAM-1) levels were correlated with the CEA level in colorectal cancer patients [37]. The CEA stimulates the monocytes and macrophages to release proinflammatory cytokines and activate the endothelium, which induces adhesion molecules on endothelial cells and eventually facilitate the metastasis of malignant cells in colorectal carcinoma [38].

Markers of inflammation, a well-recognized manifestation of oxidative stress, have also been observed to increase in response to intermittent elevated glucose levels. In the recent years there are so many evidences in the literature that metabolic syndrome and diabetes and related predisposing risk factors have close association with the risk of cancer cases. As already postulated that the mammary epithelium damage by ROS can lead to fibroblast proliferation, epithelial hyperplasia, cellular atypia, and ultimately breast cancer [39]. In this study we confirm the association between CEA & glycemic control of diabetic. We also found correlation between MDA and CEA among diabetic female in comparison to control subjects. It can be presumed the severe oxidative stress condi-

tion among untreated or poor glycemic control that may affect the incidence of risk breast cancer or other cancer among diabetic females.

Moreover there is increasing the utilization of test performed for screening purpose in the diagnostic setting in the form of battery of clinical laboratory tests. Keeping in the view, exactly to find out the relevancy of such test among diabetic females for screening for cancer along with specific markers like CEA and CA15.3, CA19.9, CA125 with MDA, a possible combination to rule out early stage.

Conclusion

In this study we confirm that CEA influence with components of type 2 diabetic and glycemic control. In this study we find correlation with Lipid peroxidation with CEA among diabetic female in comparison to control subjects. Our findings collectively suggest that CEA may be a mediator that links metabolic disturbance and tumorigenesis in diabetic. Even then with all speculations; we are unable to draw a clear cut conclusion. Still we feel the necessity to elucidate the exact mechanism involved in future studies.

Limitation of the study

We would express the possible limitations to our study. The results of this study are based on a relatively few number of diabetic females and we did not assess other possible diabetic complication of subjects. There are some factors which may affect the measurement like sample storage for longer duration. At our end it was not possible to consider all probable confounding factors.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Marghoob Hasan, Department of Medical Laboratories, College of Applied Medical Sciences, Qassim University, Kingdom of Saudi Arabia, P. O. Box 6699 Buraidah 51452, Saudi Arabia. Tel: +966564836298 Ext. 4179; E-mail: mhasanss11@gmail.com

References

- [1] Lin Y, Sun Z. Current views on type 2 diabetes. *J Endocrinol* 2010; 204: 1-11.

- [2] Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. *Ann Saudi Med* 2011; 31: 19-23.
- [3] Giovannucci E, Harlan DM, Archer MC, Bergsten RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674-1685.
- [4] Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocratol Cancer* 2009; 16: 1103-1123.
- [5] Park JS, Kim HS, Park HM, Kim CH, Kim TG. Efficient induction of anti-tumor immunity by a TAT-CEA fusion protein vaccine with poly (I:C) in a murine colorectal tumor model. *Vaccine* 2011; 29: 8642-8648.
- [6] Gür T, Demir H, Kotan MÇ. Tumor markers and biochemical parameters in colon cancer patients before and after chemotherapy. *Asian Pacific J Cancer Prev* 2011; 12: 3147-50.
- [7] Thomas P, Toth CA, Saini KS, Jessup JM, Steele G Jr. The structure, metabolism and function of the carcinoembryonic antigen gene family. *Biochim Biophys Acta* 1990; 1032: 177-189.
- [8] Ruibal Morell A. CEA serum levels in non-neoplastic disease. *Int J Biol Markers* 1992; 7: 160-6.
- [9] Lee JW, Park KD, Im JA, Hwang HJ, Kim SH. Serum carcinoembryonic antigen is associated with metabolic syndrome in female Korean non-smokers. *Clin Chim Acta* 2011; 412: 527-30.
- [10] Ishizaka N, Ishizaka Y, Toda E, Koike K, Yamakado M, Nagai R. Are serum carcinoembryonic antigen levels associated with carotid atherosclerosis in Japanese men. *Arterioscler Thromb Vasc Biol* 2008; 28: 160-165.
- [11] Kim KN, Joo NS, Je SY, Kim KM, Kim BT, Park SB, Cho DY, Park RW, Lee DJ. Carcinoembryonic antigen level can be overestimated in metabolic syndrome. *J Korean Med Sci* 2011; 26: 759-764.
- [12] Wright E Jr, Scism-Bacon JL, Glass LC. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int J Clin Pract* 2006; 60: 308-314.
- [13] Hasan M, Al Zohairy M, Mohieldin A. Diabetic type 2 and breast cancer marker CA 15.3 value. *European Journal of Experimental Biology* 2014; 4: 178-181.
- [14] Benchimol S, Fuks A, Jothy S, Beauchemin N, Shiota K, Stanners CP. Carcinoembryonic antigen, a human tumor marker, functions as an intercellular adhesion molecule. *Cell* 1989; 57: 327-334.
- [15] Malati T. Tumour markers: An overview. *Indian J Clin Biochem* 2007; 22: 17-31.
- [16] Nishida C. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157-63.
- [17] Bae U, Shim JY, Lee HR, Shin JY. Serum carcinoembryonic antigen level is associated with arterial stiffness in healthy Korean adult. *Clin Chim Acta* 2013; 415: 286-289.
- [18] Kengne AP, Limen SN, Sobngwi E, Djuogo CF, Nouedoui C. Metabolic syndrome in type 2 diabetes: comparative prevalence according to two sets of diagnostic criteria in sub-Saharan Africans. *Diabetol Metab Syndr* 2012; 4: 22.
- [19] Chen PC, Lin HD. Reversible high blood CEA and CA19-9 concentrations in a diabetic patient. *Libyan J Med* 2012; 7: 19572.
- [20] Lee JY, Lee HK, Lee DC, Lee JW. Serum carcinoembryonic antigen is associated with abdominal visceral fat accumulation in female Korean nonsmokers. *PLoS One* 2012; 7: e43518.
- [21] Guo Q, Kang M, Zhang B, Chen Y, Dong X, Wu Y. Elevated levels of CA 19-9 and CEA in pancreatic cancer-associated diabetes. *J Cancer Res Clin Oncol* 2010; 136: 1627-1631.
- [22] Ure O, Ata N, Kucukazman M, Tural E, Caglar F, Hokkaomeroglu M, K Akin K, Dal K, Yilmaz Y, Kizilca G, Beyan E, Ertugrul D. Glycemic control influences CA19-9, CEA and ferritin levels in type 2, diabetes. *Endocrine Abstracts* 2012; 29: 512.
- [23] Giacco F, Brownlee M. Oxidative stress and diabetic complication. *Circ Res* 2010; 107: 1058-1070.
- [24] Bitla AR, Reddy EP, Sambasivaih K, Suchitra MM, V Reddy S, Srinivasa R, V.L.N. Evaluation of Plasma Malondialdehyde as a Biomarker in Patients with Carcinoma of stomach. *Biomedical Research* 2011; 22: 63-68.
- [25] El-Wassef M, Gamila S, El-Saeed M, Safinaz E, El-Tokhy, Raslan HM, Tawfeek S, Ibrahim S, Salem SI. Oxidative dna damage in patients with type 2 diabetes mellitus. *Diabetologia Croatica* 2012; 41-4: 121-127.
- [26] Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal oxidative medicine and cellular longevity. *Oxid Med Cell Longev* 2014; 2014: 360438.
- [27] Shinde SN, Dhadke VN, Suryakar AN. Evaluation of Oxidative Stress in Type 2 Diabetes Mellitus and Follow-up Along with Vitamin E Supplementation. *Indian J Clin Biochem* 2011; 26: 74-77.
- [28] Karbownik-Lewinska M, Gesing A, Zasada K, Jedrzejczyk M, Sobieszczanska-Jablonska A, Krawczyk J, Kokoszko-Bilska A, Zygmunt A, Lewinski A. Relationship between lipid peroxidation or carcinoembryonic antigen and risk factors for non-communicable diseases in women

CEA and oxidative stress parameters among diabetic females

- at midlife and beyond. *Neuro Endocrinol Lett* 2012; 33: 536-45.
- [29] Niedernhofer LJ, Daniels JS, Rouzer CA, Greene RE, Marnett LJ. Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. *J Biol Chem* 2003; 278: 31426-31433.
- [30] Stattin P, Björ O, Ferrari P, Lukanova A, Lenner P, Lindahl B, Hallmans G, Kaaks R. Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007; 30: 561-7.
- [31] Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schünemann HJ, Ram M, Freudenheim JL, Sieri S, Trevisan M, Berrino F. Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 1361-8.
- [32] Dalamaga M. Obesity, insulin resistance, adipocytokines and breast cancer: New biomarkers and attractive therapeutic targets. *World J Exp Med* 2013; 3: 34-42.
- [33] Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, Eppler E, Reinecke M. Mechanisms of β -cell death in type 2 diabetes. *Diabetes* 2005; 54 Suppl 2: S108-13.
- [34] Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 2004; 27: 813-823.
- [35] Van Greevenbroek MM, Schalkwijk CG, Stehouwer CD. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth J Med* 2013; 71: 174-87.
- [36] Greenfield JR, Campbell LV. Relationship between inflammation, insulin resistance and type 2 diabetes: 'cause or effect'? *Curr Diabetes Rev* 2006; 2: 195-211.
- [37] Alexiou D, Karayiannakis AJ, Syrigos KN, Zbar A, Kremmyda A, Bramis I, Tsigris C. Serum levels of E-selectin, ICAM-1 and VCAM-1 in colorectal cancer patients: correlations with clinicopathological features, patient survival and tumour surgery. *Eur J Cancer* 2001; 37: 2392-7.
- [38] Ko IG, Park EM, Choi HJ, Yoo J, Lee JK, Jee YS. Proper exercise decreases plasma carcinoembryonic antigen levels with the improvement of body condition in elderly women. *Tohoku J Exp Med* 2014; 233: 17-23.
- [39] Aghvami T, Djalali M, Keshavarz A, Sadeghi MR, Zeraati H, Yeganeh HS, Negahdar M. Plasma level of antioxidant vitamins and lipid peroxidation in breast cancer patients. *Iranian J Publ Health* 2006; 35: 42-47.