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RESEARCH ARTICLE

SIGNIFICANCE OF CEA IN DIABETES MELLITUS TYPE 2

Yuthika Agrawal[1]., Vipin Goyal[2] and Abhishek Singh[3]

[1]Department of Biochemistry, SHKM, GMC, Nalhar, Mewat
[2]Department of Chest and TB, SHKM, GMC, Nalhar, Mewat
[3]Department of Community Medicine, SHKM, GMC, Nalhar, Mewat

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ABSTRACT

Background: Carcinoembryonic antigen (CEA) is a glycoprotein shown to be over expressed in adenocarcinomas especially of colorectal cancer. Recent research indicates that CEA-cell adhesion molecules (CEACAMs) play an important role in signal transduction and CEACAM1 is an important candidate molecule that may cause insulin resistance. It has also been reported that CEACAM1 interacts with other CEACAM protein family members like CEA (CEACAM5) and even both of them share the interacting genes. Objective was to study serum CEA levels in diabetics and determine its significance in type 2 DM, which has never been done before in India.

Material and Methods: 150 non smoker diabetic individuals divided equally into obese and non obese groups were taken along with 50 controls. Serum CEA, Serum insulin, HbA1c, fasting, post prandial sugar levels and lipid profile were also done in all diabetics.

Results: There was a significant difference between the mean CEA values in control and cases ($p< 0.001$), while there was not much difference between the CEA values in obese and non-obese diabetics. CEA values correlated with insulin (r^2=.756,p=<.001), HbA1c (r^2=.029, p=.022), HOMA-IR (r^2=.348, p<.001), fasting blood glucose (r^2=.053, p=.002), postprandial sugar (r^2= .197, p<.001), TGL (r^2=.103, p=.001), serum cholesterol (r^2= .149, p<.001), HDL (r^2=.077, p<.001) and LDL (r^2=.099, p<.001).

Conclusion: This data supports that increased CEA levels (though not several folds as in cancers) is related to diabetes irrespective of obesity suggesting that CEA functions in the pathophysiology of diabetes, possibly by heterotypically binding to hepatic CEACAM1 that are involved in regulation of systemic insulin concentration.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-communicable diseases globally.[1] The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 371 million in 2012. Based on current trends, the international Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030.[2] India is ranked second in the world in diabetes prevalence. In 2011, International Diabetes Federation estimated that India has 61.3 million people living with diabetes.[3]

Type 2 DM refers to a group of common metabolic disorders having insulin resistance with relative insulin deficiency or insulin secretory defect.[1] In response to physiologic stimuli, insulin is secreted from the pancreatic β-cells into the portal circulation in a pulsatile manner. Through its first passage, approximately 50% of the secreted insulin is cleared in the liver. Insulin clearance in liver is a critical regulator of insulin's action. Receptor-mediated insulin endocytosis and degradation in the hepatocyte underlie the basic mechanism of insulin clearance. Impaired insulin clearance can be the primary cause of insulin resistance by causing downregulation of insulin receptors and hepatic lipogenesis. Abnormalities of this insulin clearance are present in various pathological conditions including type 2 diabetes and severe obesity.[4]

Insulin action is mediated mainly by the propagation of insulin signalling through intracellular pathways involving a cascade of phosphorylation and dephosphorylation events.[5] Binding of insulin to its cell surface receptor is essential to mediate its action, where it activates tyrosine kinase to cause its phosphorylation and that of other endogenous substrates.[4]

The human carcinoembryonic Ag (CEA) family is composed of 29 genes tandemly arranged on chromosome 19q13.2.[6] The seven CEACAM (CD66) antigens (CEACAM1-8 except 2) differ in the number of immunoglobulin (Ig)-like domains, sugar content, presence of isoforms, tissue distribution and

form of membrane attachment (transmembrane region or GPI anchor). CEACAMs with a transmembrane region possess a cytoplasmic domain with or without the immunoreceptor motifs. The structural diversity of CEACAMs results in their multifunctionality, especially displayed in calcium independent homo- and heterotypic adhesion interactions.[7]

CEACAM5, which is commonly known as CEA is a 180- to 200-kDa glycoprotein that is a widely used tumor marker. CEA is overexpressed in adenocarcinoma, especially colorectal cancer, in many nonneoplastic conditions including smoking, inflammatory bowel disease, and chronic hepatitis.[7]

Recent studies have reported a positive association between CEA and cardiometabolic diseases including carotid atherosclerosis, visceral obesity and metabolic syndrome. Although CEA stimulates monocytes and macrophages to trigger the production of proinflammatory cytokines and adhesion molecules during the development of atherosclerosis, insulin resistance (IR), which is the integral part of diabetes, the precise mechanism underlying the relationship between CEA and diabetes diseases remains unclear.[8] Recent research also indicates that CEACAMs play an important role in signal transduction especially of insulin.[9]

Therefore role of CEACAMs and CEA in type 2 DM must be further evaluated. However, no study in India till date has evaluated the levels of CEA in diabetes mellitus type 2. Also no study till date from across the world, to the best of our knowledge has investigated its relation with serum insulin levels in type 2 DM. The present study was planned to investigate the serum CEA levels in type 2 DM and to correlate serum CEA concentration and serum insulin concentration in non-smoker type 2 diabetes mellitus.

MATERIAL AND METHODS

The present study was done during 2012-2013 among the patients attending diabetic clinic in PGIMS, Rohtak. Diabetes type was diagnosed according to ADA criteria. 150 non smoker diabetic individuals divided equally into obese (BMI≥30 kg/m^2) [group I] and non obese groups (BMI<30 kg/m^2) [group II] were taken along with 75 controls [group III]. Serum CEA was measured by chemiluminescence immunoassay. Serum insulin was done by ELISA. HbA1c, fasting, post prandial sugar levels and lipid profile were also done in all diabetics. Homeostasis model for insulin resistance was calculated as:[10]

$$\text{HOMA IR} = \frac{\text{Fasting blood Glucose X fasting serum insulin levels}}{405}$$

Current or former smokers, underlying medical condition including a history of chronic liver disease, chronic renal disease, coronary artery occlusive disease, postmenopausal females, hypothyroidism, chronic inflammatory disease (e.g., pancreatitis, chronic obstructive pulmonary disease) or cancer were excluded. Individuals using any medications that could affect cardiometabolic function other than oral hypoglycemics including anti-hypertensive medicine, lipid lowering agents, anti-obesity drugs, and antidepressants were also excluded. Results were analysed using appropriate statistical analysis.

RESULTS

The mean age of diabetic patients (men and pre menopausal females) was 41.46± 7.12 years, with male and premenopausal female ratio of 11:4. The mean BMI of diabetics without obesity was 26.58±0.45 kg/m^2 and that of diabetics with obesity was 32.65±1.24 kg/m^2. Basic characteristics of individuals are shown in table 1. CEA in diabetics without obesity was found to be 2.8±0.18 ng/mL which was significantly different (p<0.001) from 1.27±0.07ng/mL of controls. The CEA value in diabetics with obesity was 3.2+0.14 ng/mL, which was comparable with that of diabetics without obesity.

Table 1 Basic characteristics of diabetics taken up in the study

Parameter	Value
Mean age	41.46± 7.12 years
Male: premenopausal female ratio	11:4
Mean BMI in diabetics without obesity	26.58±0.45 kg/m^2
Mean BMI in diabetics with obesity	32.65 ±1.24 kg/m^2

BMI: Body mass index

Serum insulin level was significantly different in cases and controls and among diabetics with obesity (13.94±0.41 mIU/L) and diabetics without obesity (12.75±0.38 mIU/L). HbA1c, fasting blood sugar, post prandial blood sugar and lipid profile differed significantly among cases and controls.

The results are shown in table 2 and figure 1,2,3. Serum CEA values correlated with insulin (r^2=.756,p=<.001) (figure 4), HbA1c (r^2=.029, p=.022), HOMA-IR (r^2=.348, p=<.001), fasting blood glucose (r^2=.053, p=.002), postprandial sugar (r^2= .197, p<.001), TGL (r^2=.103, p=.001), serum cholesterol (r^2= .149, p<.001), HDL (r^2=.077, p<.001) and LDL (r^2=.099, p<.001).

Table 2 Table showing values of various parameters

PARAMETER	DIABETICS WITHOUT OBESITY	DIABETICS WITH OBESITY	NORMAL CONTROL
CEA (ng/mL)	2.8 ± 0.18*	3.2 ± 0.14 *	1.27 ± 0.07
INSULIN (mcIU/ML)	12.75 ± 0.38*	13.94 ± 0.41 */**	6.87 ± 0.11
HbA1c (%)	7.65 ± 0.12	8.1 ± 0.24	4.8 ± 0.88
FASTING SUGAR (mg/dL)	173.40 ± 5.36	179.20 ± 8.4	107.53 ± 5.34
POSTPRANDIAL SUGAR (mg/dL)	280.0 ± 7.42	286.27 ± 9.25	190.45 ± 4.34
TRIGLECERIDE (mg/dL)	177.07 ± 10.20	190.13 ± 10.76	105.63±30.15
CHOLESTEROL (mg/dL)	168.53 ± 5.2	172.60 ± 5.72	142.08 ± 4.54
HDL–C (mg/dL)	38.07 ± 1.06	35.40 ± 1.02	38.80±8.91
LDL-C (mg/dL)	94.73 ± 3.37	99.40 ± 3.40	91.57±21.25
VLDL–C (mg/dL)	35.07 ± 2.05	37.87 ± 2.15	21.12 ± 30.15

*significant w.r.t. controls, ** significant w.r.t. non-obese diabetics

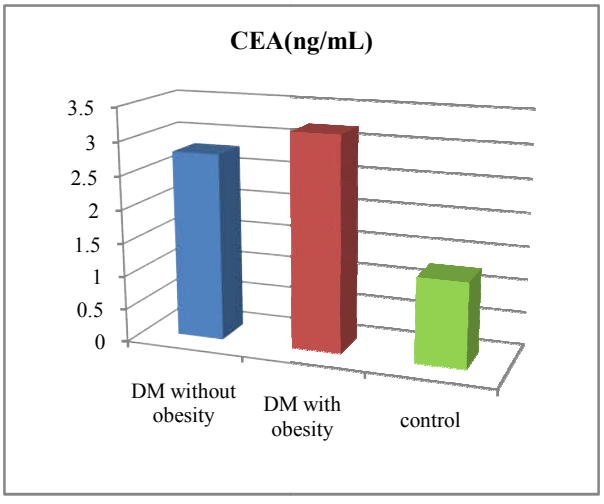

Figure 1 CEA levels in different groups

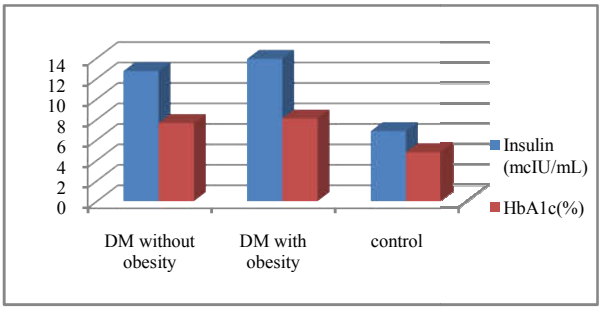

Figure 2 Insulin and HbA1c levels in different groups

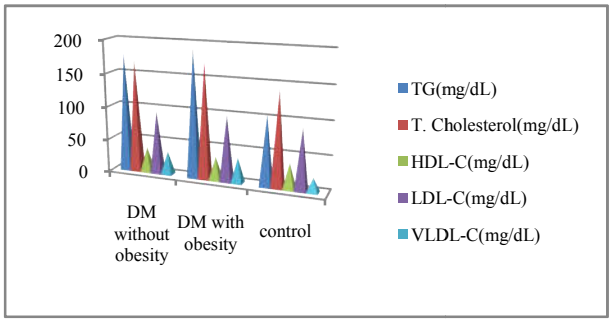

Figure 3 Serum lipid levels in different groups

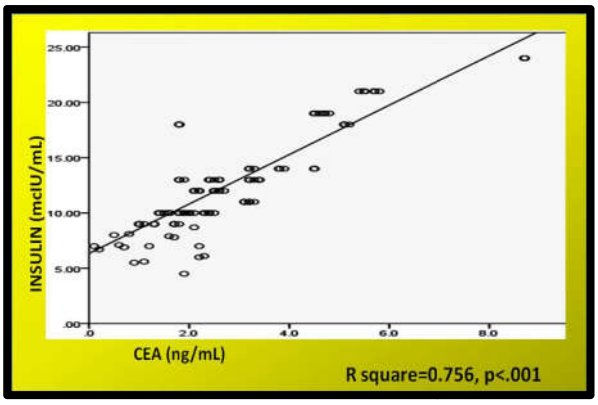

Figure 4 Graph showing correlation between serum CEA and serum insulin

DISCUSSION

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface glycoprotein. It is one of the most widely used tumor markers worldwide and is over-expressed in adenocarcinomas of colon and of other organs including the pancreas, lung, prostate, urinary bladder, ovary and breast.[7] 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.[11] 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.[12] MS confers a greater risk of type 2 diabetes.[13] Pei-Chi Chen *et al*[14] reported a case of diabetic male with elevated CEA level. Also, Jeep-Yon Lee *et al*[15] found statistically significant levels of serum CEA level in around 8% diabetic Korean female's subjects. Another study, reported elevated level of CEA in pancreatic cancer-associated diabetes.[16]

To our knowledge, there are only these above mentioned four studies which have investigated CEA levels in DM and found higher CEA levels in diabetics than controls but none of them have investigated relation between serum insulin and CEA in DM type 2. [14,15,17,18] No study till date, has investigated serum CEA relation with serum insulin levels in type 2 DM. and also to best of our knowledge, no study in India has evaluated the role of CEA in diabetes. In our study serum CEA levels in diabetics without obesity was found to be 2.8±0.18 ng/mL and 3.2+0.14 ng/mL in diabetics with obesity. Though these levels were near normal reference range of 0-2.5 ng/mL but were still significantly different ($p<0.001$) from mean serum CEA level of 1.27±0.07ng/mL found in our controls. Thus our cross-sectional study reveals a relationship between serum CEA level and diabetes mellitus, as serum CEA levels were significantly different in type 2 diabetics as compared to controls and also correlated with serum insulin and HOMA-IR in diabetics.

Previous studies have shown serum CEA to be positively associated with metabolic syndrome in a concentration-dependent manner and serum CEA levels has also been reported to be influenced by obesity,[12,15] therefore we evaluated serum CEA levels in both diabetics with obesity and those without it, in order to exclude the effect of obesity on serum CEA in DM. The precise underlying mechanisms that explain the relationship between serum CEA concentration and visceral obesity remains unclear. Furthermore, Nobukarzu *et al*[19] also reported a positive relationship between carotid atherosclerosis and serum CEA concentration. Our study shows no significant difference in the serum CEA levels in obese and non-obese type 2 diabetics.

Whether CEA levels and diabetes are directly associated, or if this relationship is mediated by other environmental factors, has not yet been figured out. Therefore, additional basic experimental studies are warranted. However, we propose some possible mechanisms for this relationship.

First, CEA consists of an Ig V-like N-terminal domain followed by three pairs of Ig C2-like domains that are processed to allow the addition of glycophosphatidyl- inositol membrane anchor. In addition to the homophilic interaction to itself, CEA binds heterophilically with CEACAM1. CEACAM1 binding to CEA has been shown to be direct and functional.[6]

CEACAM1 is a liver-specific transmembrane glycoprotein and it is also a substrate of insulin receptor in liver. Normally CEACAM1 is phosphorylated in response to insulin in hepatocytes and it plays a role in insulin clearance by increasing receptor-mediated endocytosis via clathrin-coated pits and targets it for degradation.[4] Upon insulin receptor activation, CEACAM1 dependent pathways mediate a decrease in FAS activity to protect the liver from the lipogenic effect of high insulin levels in portal vein.[20]

Binding of CEA to CEACAM1 causes inactivation of CEACAM1 and this CEA act as a naturally occurring activator of the CEACAM1- dependent apoptosis pathway.[9] CEACAM1, phosphorylation-defective isoforms (possibly attached to CEA) impairs insulin clearance and causes hyperinsulinemia, insulin resistance and dyslipidemia,[5] which can possibly explain the results of our study. Lack of CEACAM-1 can lead to accelerated progression toward hepatic steatosis. The ectopic fat deposition appears to be mainly explained by the induction of hepatic lipogenesis, perhaps coupled with altered HDL metabolism resulting in increased hepatic HDL cholesterol uptake, thus decreasing

HDL levels.[20] This possibly explains the correlation between serum cholesterol, HDL-C with CEA levels in DM type 2.

The greater hyperinsulinemic state can be explained by oversecretion of insulin, compensating for a more severe insulin-resistant state. Many studies suggest that hepatic lipid accumulation due to dysfunctional lipogenic/cholesterogenic enzymes or metabolic signalling pathways results in an insulin resistance phenotype. In contrast, increased cholesterol synthesis due to higher SREBP2 activity causes hepatic insulin resistance. CEACAM1 deficiency causes up-regulation of SREBP2 transcriptional pathways, leading to increased esterified cholesterol, predisposing the liver to insulin resistance and metabolic dysfunction.[20]

Another justification can be since CEA levels are associated with diverse chronic inflammatory diseases, increased inflammatory cytokines and adipokines in diabetes may stimulate the cellular expression of CEA, contributing to the development of insulin resistance.[15]Also the histology of pancreatic islets from type 2 diabetic patients was known to be associated with an inflammatory process, suggesting the presence of a subclinical, mild form of pancreatitis, which may be responsible for the temporary elevation of blood CEA.[14]

Direct association of CEA with diabetes can also be considered, as it has been reported that CEA can be secreted from non-CEA producing cells under certain conditions. Hence, we can hypothesize that alteration of cellular environment in diabetes may induce the direct expression of CEA from pancreas.[15] The increased activity of cyclic-AMP in diabetes also stimulates the synthesis and release of CEA, a membrane-associated glycoprotein antigen. In normal liver tissue, CEA accumulates in the apical cytoplasm and along the luminal surface of bile duct epithelial cells and is excreted by bile ducts.[21]

Most importantly, previous studies have shown anti-human CEA antibody Col-1, to increase akt-phosphorylation which is involved in insulin action,[22] which if further evaluated, can become an important line of treatment in DM type 2 and monoclonal antibodies against CEACAMs may provide new routes for diabetic immune therapy.

This study has several limitations. First, the cross-sectional design cannot establish a causal relationship between CEA levels and diabetes. Second consideration of assessing inflammatory cytokine and adipokine levels and CEACAM1 in study subjects, will provide additional important information in future studies. Further research is warranted in this aspect with larger sample size to understand the clinical and pathophysiological significance of CEA in type 2 DM.

CONCLUSION

In conclusion, our study showed that serum CEA is associated with insulin resistance in non-smoker diabetics. Our findings collectively suggest that CEA may be a mediator that links insulin resistance in diabetes irrespective of obesity suggesting that CEA functions in the pathophysiology of diabetes. In addition, elevation of CEA, even within the "near normal'' range, may be considered a presumptive marker for diabetes. Although serum tumor markers are infrequently determined in diabetic patients, blood CEA is occasionally measured for other reasons. We should be very careful to differentiate between the benign and malignant etiologies of the elevated tumor markers in diabetes. Monoclonal antibodies against CEACAMs may provide new routes for diabetic immune therapy. Further studies are required to better understand the clinical and pathophysiological significance of our findings.

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