International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Effect of Glycemic Status on Serum CEA and CA 19-9 Levels in Patients of Diabetes Mellitus in Northern India

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ABSTRACT

Cancer biomarkers can be used in early detection of several cancers as well as in detection of recurrence and following response to treatment. Glycemic status of diabetic patients can influence the serum levels of these markers even in the absence of malignancy. In the present study we aimed to investigate the effect of glycemia on the levels of two tumor markers CEA and CA 19-9. A total of 100 subjects were enrolled in the study, 50 patients of poorly controlled Diabetes Mellitus and 50 healthy controls. We measured fasting plasma glucose, HbA1c, lipid profile (total cholesterol, triglycerides and HDL cholesterol), serum CA 19-9 and serum CEA levels with an automatic analyzer in all the subjects. Fasting plasma glucose (FPG), HbA1c, serum CEA, CA 19-9 and triglycerides were significantly higher in the study group compared to controls. Serum CEA showed a significant positive correlation with FPG and HbA1c and a significant negative correlation with HDL-C levels whereas serum CA 19-9 showed a significant positive correlation only with FPG. We propose to formulate a higher cut off of CEA and CA 19-9 in diabetic subjects considering the effects of hyperglycemia, to avoid further invasive investigations.

Keywords: Diabetes Mellitus; CEA; CA 19-9; Lipid Profile

INTRODUCTION

Tumor markers such as CA 19-9 and CEA are closely related with gastrointestinal (GI) cancers and are used in their screening. Several benign conditions can also elevate these tumor markers such as hepatobiliary system inflammation, hydronephrosis, thyroid disease, acute and chronic pancreatitis and pulmonary disease. [1-4]

Incidence of GI and pancreatic cancers are increased in diabetes mellitus (DM). [5] Pancreatic cancer may be considered as one of the several complications of DM. There is a complex relation between pancreatic cancer and DM whose aetiology has not been identified yet. A meta-analysis of 20 studies found a two-fold increased risk of pancreatic cancer among diabetic patients of 5 years duration, suggesting that diabetes is a risk factor for the tumor. [6] Others have concluded that cancer preceded and caused diabetes. [7] Some studies even suggest that DM protects against pancreatic cancer. [8]

There is scarce information in the literature regarding the effect of glycemia on these tumor markers in the absence of a tumor. Few studies have indicated a significantly higher level of CA 19-9 in

patients of DM than controls. However, others did not find a correlation. And very few studies have been conducted on CEA levels in DM with variable results. Further, none of the studies have been conducted on Indian population.

So, the present study was conducted with an aim to evaluate serum CEA and CA 19-9 levels in patients of poorly controlled diabetes mellitus in comparison with age and sex matched healthy control subjects in North India. In addition, we aimed to find out any correlation between these tumor markers, glycemic status of a subject and parameters of lipid profile in diabetic subjects.

MATERIALS AND METHODS

The study was performed using case control design. 50 subjects of DM visiting the OPD's of G B Pant Hospital, New Delhi and 50 healthy individuals were enrolled in this cross-sectional study. Detailed clinical history and informed consent was taken. Individuals with malignancy, history of chemotherapy or radiotherapy, acute or chronic pancreatitis, smoking were excluded. Individuals with diabetes who have any co-existent factor leading to raised CEA or CA 19-9 were also excluded. Abdominal USG and CT scan (where required), was done to rule out abdominal malignancy.

Fasting blood sample was collected from all the subjects to test for plasma glucose, serum CA 19-9, serum CEA, HbA1c and lipid profile (total cholesterol, triglycerides and HDL-Cholesterol).

Plasma glucose (GOD-POD method), serum total cholesterol (Cholesterol oxidase-peroxidase), serum triglycerides (glycerophosphate oxidase-peroxidase) and HDL-C (Direct homogenous) were estimated on fully automated analyser by Roche-Cobas 611. HbA1c was estimated by HPLC on Biorad D-10. CEA and CA 19-9 were measured on Roche e411 by electro-chemiluminescence technique. Cut off of 37 U/L was set for CA 19-9 and 5 U/L was set for CEA above which the results were considered as abnormal.

Statistical Analysis

The data was reported as mean ± SD. The chi²-test was applied for comparison of categorical variables and the t-test was applied for comparison of continuous variables between cases and controls. The Pearson and Spearman correlation coefficients were calculated to assess the strength of the correlation of CEA and CA19-9 with other parameters $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (Version 12.0, Chicago, IL, USA).

OBSERVATIONS AND RESULT

50 diabetic patients and 50 healthy controls were involved in the study. These two groups were similar in terms of age and gender. The biochemical measurements for the two groups have been summarised in Table I.

Table I - Biochemical parameters studied in the two groups

Parameter	Study group	Control group	Significance	
	Mean ± SD	Mean ± SD	p value	Sig
FPG (mg%)	200 ± 97	97.6 ± 9.79	0.0001	S
HbA1c (%)	9.0 ± 2.3	5.6 ± 0.5	0.0001	S
CEA (U/L)	3.5 ± 2.1	1.7 ± 0.84	0.0002	S
S. CA 19-9 (U/L)	16.5 ± 12.1	7.8 ± 5.7	0.001	S
Total Cholesterol (mg%)	166.8±51.1	176 ± 44.2	0.47	NS
Triglycerides (mg%)	163.4 ± 72.9	130.1 ± 50.9	0.049	S
HDL-C (mg%)	40.6 ± 8.2	42.2 ± 11.7	0.55	NS

FPG and HbA1c was significantly higher (p=0.0001) in the study group compared to control subjects. Serum CEA levels (p= 0.0002) and CA 19-9 levels (p = 0.001) were significantly higher in diabetic patients compared to healthy controls. Among

parameters of lipid profile, only serum triglycerides (p <0.05) was significantly higher in diabetics compared to controls.

Table II - Correlation of CEA levels with different parameters in the study group

	Parameter	Correlation coefficient (r value)	Significance (p value)	
S. CEA	FPG	0.448	0.015	S
	HbA1c	0.525	0.003	S
	T. Cholesterol	-0.084	0.666	NS
	Triglycerides	0.013	0.945	NS
	HDL-C	-0.409	0.028	S

As seen from Table II, there was a significant positive correlation between CEA and FPG(r = 0.448, p= 0.015) and HbA1c (r = 0.525, p=0.003). Amongst the lipid profile, only HDL-C showed a significant negative correlation with CEA levels (r = -0.409, p=0.028).

Table III - Correlation of CA 19-9levels with different parameters in the study group

	Parameter	Correlation coefficient (r value)	Significance (p value)	
S.CA 19-9	FPG	0.50	0.006	S
	HbA1c	0.264	0.167	NS
	T. Cholesterol	0.033	0.867	NS
	Triglycerides	0.033	0.864	NS
	HDL-C	-0.084	0.667	NS

As observed from Table III, S.CA 19-9 levels only showed a significant positive correlation with FPG (r value – 0.50, p=0.006). With HbA1c, the correlation was positive but not significant (r = 0.264, p = 0.167). No significant correlation was found between S.CA 19-9 and serum cholesterol, triglycerides or HDL-C levels.

DISCUSSION

Our study demonstrated significantly raised levels of both CEA and CA 19-9indiabetic patients of North India compared to control group. Further it revealed a significant positive correlation of both the tumor markers with fasting plasma glucose. CEA levels showed a significant positive correlation with HbA1c. However, CA 19-9 showed a statistically non-significant but positive association with HbA1c which might be due to the smaller sample size.

Similar results were observed by O. Ure et al who showed that FPG and HbA1c showed a significant positive correlation with CEA and CA 19-9levels. [9] Naim Ata et al studied the levels of CEA and CA 19-9 before and after glucose control by administering insulin to patients. They found that basal CEA and CA 19-9 levels have a significant positive correlation with FBG and HbA1c and their levels decreased significantly after glycemic control. However, even after glycemic control, the levels of tumor markers were still higher in the diabetic group compared to healthy controls. [10] Benhamou et al had previously found a significant correlation between fasting blood glucose, HbA1c, and CA 19-9 levels. [11] Gul et al showed that serum CA 19-9 level was related to microvascular complications in type 2 DM patients. [12] Jung-Im No et al observed a positive correlation of CEA with fasting glucose, HbA1c and HDL cholesterol in both males and females. [13]

In contrast, Banfi et al found no correlation between Ca 19.9 and glycemia in diabetic subjects. [14] Another study by Turgutalp K et al, investigating CEA levels in diabetes mellitus, found lower CEA levels in diabetics than controls. [15]

Diabetes has been claimed to be a risk factor for pancreatic cancer, which is increasing its incidence and has one of the lowest survival rates of all cancers. Chronic pancreatitis and DM are both risk factors for pancreatic cancer. [16] DM is a chronic inflammatory disease of the pancreas. Glucose intolerance is caused by insulin resistance and destruction of islet beta cells. Most of these conditions damage the exocrine tissue along with the islet cells, as both of these are anatomically and functionally related. There are no capsules or basement membranes around islets and there are cell to cell contacts between the exocrine and endocrine cells. [17] Inversely, chronic pancreatitis is often associated with endocrine pancreatic dysfunction, causing a secondary form of diabetes, which accounts for <1% of all DM cases. Approximately 80

% of patients with chronic pancreatitis develop an overt DM in their lifetime, and DM is also an independent risk factor for mortality in patients with chronic pancreatitis. [18, 19]

CEA and CA 19-9 levels are elevated in gastrointestinal malignancies. [20] The elevation of these markers in diabetic patients might be related to the interaction between exocrine and endocrine pancreatic cells. HbA1c is a marker of chronic glucose toxicity. The association between these tumor markers and HbA1c may be a sign for potential neoplastic proliferation in hyperglycemic environment. The lack of insulin could result in a pancreatic exocrine deficiency and release of CA 19-9 by ductal cells. [21] Therefore, the increase of serum CA19-9 level might parallel the intensity of cellular functional disorders. Many early studies on pancreatic function in diabetes demonstrated that pancreatic exocrine insufficiency is present in a considerable percentage of patients with diabetes. Autopsy studies and studies on pancreatic histology have shown presence of marked chronic inflammatory changes of the exocrine pancreas in diabetic patients compared to non-diabetic controls. [22,23]

Another contributory factor to increased CEA levels in our study is that CEA levels are affected by metabolic syndrome of which impaired glucose tolerance and insulin resistance are components. A study by Kim K-N et al, revealed that increasing sum of metabolic syndrome components were significantly associated with linear increasing trends in CEA. [24] The possible explanation is that insulin effects growth of normal and neoplastic epithelial cells and has mitogenic actions in-vitro either directly or through IGF-1. Thus, IR in diabetes may be associated with increase of CEA. [25] Similar results were observed by Lee et al in North Korean Females. [26]

Diabetes is also accompanied by abnormal blood lipid profile. Our study has revealed a significant negative correlation of CEA with HDL-C similar to that observed by Kim K-N et al. [24] We did not observe any correlation between CA 19-9and parameters of lipid profile, which is in consensus with the study conducted by Nakamura et al [27] but in contrast to that observed by Haoyong Yu et al. They observed that CA 19-9 correlated positively with total cholesterol. The observed link might be due to the lipotoxic effect of intracellular cholesterol on pancreatic beta cell function. [28] However further work is required to establish an association between lipid profile and tumor markers and to unfold the etiology.

In conclusion, our study reports a positive association between DM and elevated levels of CEA and CA 19-9. This is the first study to be conducted in Indian population. In individuals with elevated levels of these tumor markers, hyperglycemia should be kept in mind as a potential confounder. A higher cut-off for CEA and CA 19-9 can be defined in diabetics to prevent unnecessary laboratory and imaging procedures.

A limitation of the present study is that it is a cross-sectional study. A long term follow-up study of these subjects should be undertaken to determine whether elevated levels of CEA and CA 19-9 is a pre-cancerous state or a mere benign condition causing confusion for the clinician. Another limitation of the study is that being a cross sectional study, we are unable to comment on the effects of glycemic control on these tumor markers for which further studies are required.

Conflict of Interests: The authors declare that they have no conflict of interests.

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How to cite this article: Singla R, Goyal A, Mahajan B et al. Effect of glycemic status on serum CEA and CA 19-9 levels in patients of diabetes mellitus in northern India. Int J Health Sci Res. 2018; 8(2):67-72.

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