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Original Research Article

Relationship between plasma calcium and carcinoembryonic antigen among colorectal cancer patients

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ABSTRACT

Background: Low serum calcium is hypothesized to influence colorectal carcinogenesis. Hence, this study was set out to investigate the pattern of plasma calcium in patients with colorectal cancer, and to determine the relationship between the mineral with carcinoembryonic antigen (CEA) among patients with colorectal cancer.
Methods: This was a retrospective study of 45 colorectal cancer patients who presented to a tertiary hospital in Nigeria. The laboratory characteristics of these patients were evaluated. Records of sex, age, serum albumin, plasma total calcium, and serum CEA test results from 1st January 2008 to 31st December 2017 were retrieved from laboratory and medical records and analyzed with SPSS software version 20.
Results: There were a total of 45 records of colorectal patients in this study, among them were 62.2% males and 37.8% females. The majority (57.8%) of the study cohorts are within the age group 50 to 59 years. Low total calcium was observed in 37.8% of the study cohort while 66.7% tested positive for CEA. The positive CEA group had lower total calcium level than those with negative CEA results ($p = 0.001$). Negative but weak correlations of total calcium and serum CEA was observed among the overall study cohort ($r = -0.485$; $p = 0.001$) and those with positive test for CEA ($r = -0.384$; $p = 0.036$).
Conclusions: The evidence from this study suggests that low serum calcium could be a risk factor for colorectal cancer and is also associated with higher serum level of the CEA biomarker.

Keywords: Colorectal cancer, Calcium, Carcinoembryonic antigen, Nigeria

INTRODUCTION

Colorectal cancer is the third most common cancer diagnosed worldwide and the disease accounts for a very high proportion of cancer mortality globally.[1] The incidence of the disease is relatively low in Nigeria, however, some authors have recently reported that its incidence is gradually increasing due to the rapid westernization of dietary lifestyle inherent in the country.[2]

The influence of genetic, hereditary, environmental, and nutritional factors have all been suggested to increase the risk of colorectal cancer incidence globally.[2-5]Among the suggested nutritional factors is the influence of low plasma calcium in the evolution and progression of the disease.[6-8] This postulation of low plasma calcium influence on colorectal cancer incidence stem from numerous observational and experimental studies implicating low level of the mineral as a culprit in colorectal carcinogenesis.[9-11]

The diagnosis of colorectal cancer entails medical history, clinical examination, radiological, and laboratory investigation protocols using biomarkers.[12] Serum carcinoembryonic antigen (CEA) is the most common biomarker employed in the laboratory investigation of colorectal cancer including in the screening, diagnosis, prognostication, and monitoring of treatment and recurrence in patients with the disease.[13-16] The CEA biomarker was first described in 1965 by Gold and Freedman in relation to colon cancer and its high serum level have been suggested to parallel colorectal cancer burden, stage, grade, and metastatic potential.[13-18]

The relationship between low plasma calcium and CEA in colorectal is scarce in the literature. However, Fuszek et al had recently reported a null correlation between serum calcium and CEA among colorectal cancer patients.[9] Hence, the relationship between serum calcium and CEA warrants further investigation.

Therefore, this study was instituted to highlight the pattern of plasma calcium status in colorectal cancer patients and to evaluate the relationship of the mineral with serum level of CEA. Specific objectives were to determine the pattern of plasma calcium in these patients with colorectal cancer, determine the pattern of carcinoembryonic antigen (CEA) among these patients with colorectal cancer, to determine the sex and age distribution of the disease among the study cohorts, and to compare this study with similar studies in the literature.

METHODS

This study was conducted in the Department of Chemical Pathology and Metabolic Medicine of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria, West Africa. The Department of Chemical Pathology and Metabolic Medicine is the cancer screening center of the hospital.

It is a retrospective, descriptive, cross-sectional study conducted between 12th November 2017 and 20th February 2018. Records (sex, age) and the laboratory parameters (plasma albumin, plasma total calcium, and serum CEA) of colorectal cancer patients irrespective of cancer stage who presented to the department over a 10-year period (1st January 2008 31st December 2017) were assessed and analyzed. All the colorectal cancer patients had been diagnosed by specialist surgeons in the hospital. Informed consent and ethical approval were not required owing to the retrospective design of the study.

Inclusion criteria

Inclusion criteria include all the aforementioned records and laboratory parameters of the treatment-naïve colorectal cancer patients irrespective of the stage of the disease who presented to the department during the study period.

Exclusion criteria

Exclusion criteria include all the records and laboratory parameters of the colorectal cancer patients who are already on treatment (medical, surgical or radiotherapy), those that are cigarette smokers and those with incomplete medical records.

During the study period, plasma samples had been used for calcium analysis using the colorimetric method, plasma albumin analyzed using the bromcresolgreen (BCG) method, and serum CEA was analyzed using the enzyme immunoassay method. During all the analytical procedures, accuracy was strictly ensured by the use of three levels of commercial quality control sera.

Data were retrieved from the laboratory records and case notes of each patient and entered into Statistical Package for Social Sciences (SPSS) version 20. Data on demographics (Age and sex), plasma albumin in g/l (normal range: 36-50), total uncorrected calcium in mmol/l (normal range: 2.20-2.65), and serum CEA in ug/l (Reference threshold is 5ug/l) were recruited for the study. The total plasma calcium was subsequently corrected as albumin-corrected calcium with the following formula:

Plasma total calcium + (40 – plasma albumin in g/l) x 0.02.

Plasma albumin-corrected calcium was stratified as low (<2.20 mmol/l), normal (2.2-2.65 mmol/l), and high (>2.65 mmol/l). Serum CEA <5 ug/l was designated as been negative for colorectal cancer while >5 ug/l was designated as been positive for colorectal cancer.

The retrieved data were imported into SPSS version 20, subsequently reviewed, coded, validated and analyzed. Initially, the continuous data were tested for normality using Shapiro-Wilk statistics. Non-Gaussian distributed data was log-transform before analysis. Continuous data were presented as mean±standard deviations and compared with independent t-test, while categorical data were presented in numbers and percentages and compared using Chi-square. Pearson's correlation test was used to evaluate linear relationships between continuous data. A p-value of <0.05 was deemed statistically significant.

RESULTS

During the study period (1st January 2008 to 31st December 2017), a total of 51 treatment-naïve colorectal cancer patients presented to the Department of Chemical Pathology and Metabolic Medicine of the University of Port Harcourt for plasma calcium and carcinoembryonic antigen test. The records of 90% (45 out of 51) of the patients met the inclusion criteria and were eventually utilized for the study.

Among the 45 colorectal cancer cases were 28 (62.2%) males and 17 (37.8%) females. The mean age of study cohorts was 55.5±5.671. Age difference between males and females (males 57.7±4.372 versus females 51.9±5.868; p = 0.001) was observed among the study cohort.

Table 1: Characteristics of laboratory parameters of study cohorts.

Parameter	Mean±SD	Range
Laboratory parameters		
CEA (ug/l)	35.89±32.94	2.7-110
Albumin (g/l)	34.42±2.04	30-39
Uncorrected total plasma calcium (mmol/l)	2.15±0.92	1.94-2.33
Total plasma albumin-corrected calcium (mmol/l)	2.23±0.93	1.94-2.71

mmol/l = millimole per liter; CEA = Caecinoembryonic antigen; SD = Standard deviation; ug/l = Microgram per liter

Table 1 shows the mean±standard deviations and range of the various study laboratory parameters.

Table 2: Strata of age groups, plasma albumin-corrected calcium level, and carcinoembryonic antigen level of study cohorts.

Parameter	n (%)	p-value
Stratum of age groups		
< 49 years	10 (22.2)	0.002*
50 – 59 years	26 (57.8)	
>60 years	9 (20.0)	
Stratum of total plasma albumin-corrected calcium		
<2.20 mmol/l (Low)	17 (37.8)	0.004*
2.20-2.65 mmol/l (Normal)	23 (51.1)	
>2.65 mmol/l (High)	5 (11.1)	
Stratum of serum carcinoembryonic antigen		
<5ug/l (Negative)	15 (33.3)	0.025*
>5ug/l (Positive)	30 (66.7)	

*Statistically significant; mmol/l = millimole per liter; CEA = Carcinoembryonic antigen; ug/l = Microgram per liter

In Table 2, 57.8% (26 out of 45) of the colorectal cancer cases were in the age group of 50-59 years. Low plasma calcium was observed in 37.8% (17 out of 45) of the cases. Using the reference threshold of 5 ug/l for serum carcinoembryonic antigen test, 66.7% (30 out of 45) was positive for colorectal cancer.

In Table 3, the CEA positive group had a significantly reduced total plasma albumin-corrected calcium level than those with the negative test for CEA.

In Table 4, there were significant negative but weak correlations of total plasma albumin-corrected calcium and serum CEA among the overall study cohort and those with the positive test for CEA.

Table 3: Comparison of plasma albumin-corrected calcium level among the stratum of carcinoembryonic antigen levels.

	Stratum of serum carcinoembryonic antigen levels		p-value
	< 5 ug/l (Negative)	>5 ug/l (Positive)	
Total plasma albumin-corrected calcium level in mmol/l (Mean±SD)	2.27±0.24	2.17±0.13	0.001*

*Statistically significant; SD = Standard deviation; mmol/l = millimole per liter; ug/l = Microgram per liter

Table 4: Correlation of the plasma albumin-corrected calcium and serum carcinoembryonic antigen levels among the overall study group and the stratum of carcinoembryonic antigen.

		Correlation of total plasma albumin-corrected calcium and serum carcinoembryonic antigen	
Groups	**n (%)**	**r**	**p-value**
Overall study group	45 (100)	-0.485	0.001*
CEA <5ug/l (Negative)	15 (33.3)	-0.010	0.971
CEA >5ug/l (Positive)	30 (66.7)	-0.384	0.036*

*Statistically significant; CEA = Carcinoembryonic antigen; ug/l = Microgram per liter; r = correlation coefficient.

DISCUSSION

Colorectal cancer incidence, prevalence, and mortality are increasingly becoming a global burden.[1] It was before 1900 a rare disease in the western population but has become a common disease and continue to increase yearly in that region of the world.[19] These adverse characteristics of the disease in the western population has been attributed to factors brought about by changing dietary lifestyles inherent in that part of the world.[20]

The disease is relatively rare in the undeveloped and developing nations, but recent report has shown that the disease incidence and prevalence are increasing among the population in these underdeveloped and developing countries due to westernization of their dietary lifestyles.[2] This epidemiologic evidence underscores the importance of nutritional and dietary risk factors in the evolution of colorectal carcinogenesis.[20]

The role of calcium as a nutritional and dietary risk factor in colorectal carcinogenesis has been well-documented in the literature.[7,8] Most of these studies in the literature are mostly dietary intake prospective and experimental studies, few studies have mirrored the relationship

between calcium and colorectal cancer to the influence of endogenous calcium status on the disease.[9-11,21,22] In this study, we had evaluated the relationship between endogenous plasma calcium in diagnosed colorectal cancer patients and observed a 37.8% rate of low plasma calcium level (hypocalcaemia) among these patients.

The reported rate of hypocalcemia in this patients is higher than the 11.53% prevalence rate of hypocalcemia reported among Nigerian patients attending a tertiary hospital by Ogunkolo et al and the 10.8% prevalence rate reported by D'Erasmo et al among ambulatory cancer patients in a hospital-based study.[23,24] This finding supports the numerous epidemiologic reports of the involvement of low plasma calcium in colorectal carcinogenesis.

Fuszek et al had investigated the relationship between calcium and various prognostic markers of colorectal cancer including CEA among colorectal cancer patients and concluded that lower calcium levels can be pathogenic and prognostic in the disease.[10] Recently Wulaningsih et al had noted a similar finding to that of Fuszek et al in their own study.[11] These reports by Fuszek et al and Wulaningsih et al are all in accord with this study where we noted a low calcium level more pronounced among those with positive CEA levels.

However, Fuszek et al had reported a null relationship (p=0.79) between this mineral and CEA in that study. This is at variance with the findings in this study where we observed a significant inverse association between serum calcium and CEA, the relationship becomes more pronounced among the cancer patients with low calcium level. The reason for this discrepancy could be related to the fact that Fuszek et al had used ionized calcium to evaluate this relationship in contrast to the total plasma calcium employed in this study.

The mechanism of calcium protective effects in colorectal carcinogenesis is ill-understood. However, several mechanisms have been suggested and reported by several authors.[25,26]

Calcium is suggested to decrease the incidence of colorectal cancer disease by directly binding to toxic intestinal mucosa metabolites (secondary bile acids and free ionized fatty acids) to form insoluble soaps in the colorectal intestinal tract, thereby reducing the effects of these metabolites on the intestinal mucosa.[25] Calcium is also proposed to reduce proliferation, enhancement of differentiation, and inducement of apoptosis in the colorectal mucosa.[26]

The limitation of the present study was that being a retrospective hospital-based study from a single center, its conclusion may not reflect the status of the entire population in our region and so must be interpreted with caution.

CONCLUSION

There is a high prevalence of hypocalcemia among patients with colorectal cancer which negatively correlates with CEA. This suggests an association between low calcium status and colorectal cancer with high serum CEA in patients with the disease and tend to support the numerous report of the link between this mineral and colorectal carcinogenesis. However, further studies with large sample size are warranted to confirm these findings.

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