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An Observational Study To Evaluate Level Of Serum Calcium And Ca 19-9 In Colorectal Carcinoma Cases

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Abstract
Introduction: *Colorectal Cancer Is A Common Cancer Worldwide. It Is The Third Most Commonly Diagnosed Cancer In Males And The Second In Females, With More Than 1.4 Million New Cancer Cases Every Year. The Age Standardized Rate (Asr) For Colorectal CancerIn India Is Low At 7.2 Per 100,000 Population In Males And 5.1 Per 100,000 Populations In Women. Several In Vitro And In Vivo Studies Have Confirmed TheChemopreventive Role Of Calcium In Colorectal Carcinoma. The Experimental Data Showed That There Was A Definite Connection Between Low Calcium And Vitamin D Intake And The Prevalence Of Colorectal Carcinoma. Carcinoembryonic Antigen(CEA) Is The Commonly Used Tumour Marker In Patients Of Colorectal CarcinomaAnd CA19.9 Might Be Used As An Additional Marker In Patients Of Colorectal Cancer.*
Aim And Objective: *To Evaluate Serum Level Of Calcium And CA 19.9 And Their Relationship In Colorectal Carcinoma.*
Material And Methods: *This Was A Hospital Based Observational Study Started From June 2019 To December 2020 Or Till The Sample Size Was Achieved At Department Of General Surgery, S.M.S. Hospital, Jaipur, Rajasthan, India. The Study Included Sample Size Of 40 Patients Whose Detailed History And Clinical Examination Was Done. Sample Size Is Calculated At 95% Confidence Interval And 0.05 Alpha Error Assuming Mean Level Of Calcium 2.26, At Expected Sd Of 0.17 As Per Seed Article Relationship Between Serum Calcium And Ca 19-9 Levels In Colorectal Cancer Peter Fuszek Et Al.*
Observations And Results: *The Study Included Sample Size Of 40 Patients Whose Detailed History And Clinical Examination Was Done. Incidence Of Colorectal Carcinoma In > 50 Years Of Age Is 47.5%. Incidence Below 50 Years Age Is 52.5%. 55.00% Cases Were Male 10% Higher Than Females. 55.00% Patients Were Smoker And 45.00% Patients Were Non Smoker. In Our Study, 42.50% Patients Present WithIntestinal Obstruction, 32.50% Patients Present With Per Rectal Bleed, 17.50% Patients Present With Abdominal Pain And Lump, 5.00% Patients Present With Abdominal Pain And Per Rectal Bleed And 2.50% Patients Present With Abdominal Lump. So, The Most Common Presentation OfColorectal Cancer In Our Study Was Intestinal Obstruction.*
Conclusion: *We Conclude That Ca19.9 Tumour Marker Had A Prognostic Role In Colorectal Cancer. Elevated Serum Levels Were Associated With The High Stage Colorectal Carcinoma Or The Presence Of Metastasis. It Supports The Significance Of Serum Calcium Not Only As A Pathogenic Factor But Also As A Prognostic Factor. So By Increasing Calcium Intake, The Multileveled Pathogenic Process Leading To Tumorigenesis Might Be Influenced But It Requires Further Research And Randomized Controlled Multicentric Trials.*
Key Words:*Serum Calcium, CA 19-9, Colorectal Carcinoma Cases.*

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I. Introduction

In recent decades, there has been an increasing prevalence of cancers in the world. Colorectal cancer is a common cancer worldwide. It is the third most commonly diagnosed cancer in males and the second in

females, with more than 1.4 million new cancer cases every year. The age standardized rate (ASR) for in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 populations in women.[1]

There are several risk factors that are associated with the development of colorectal carcinoma and some of them imply an earlier screening.[2] Age is one of the main risk factors for the development of colorectal carcinoma, with over 90% of cases occurring in individuals aged over 50 years, with a mean age of diagnosis of 65 years. For this reason, colorectal carcinoma is considered a disease of the elderly.

Several in vitro and in vivo studies have confirmed the chemopreventive role of calcium in colorectal carcinoma. The experimental data showed that there was a definite connection between low calcium and vitamin D intake and the prevalence of colorectal carcinoma.[3]

According to twin studies, serum calcium level was mostly determined by genetic factors. One of the key factors of this determination is the calcium-sensing receptor (CaSR), which by sensing the concentration of calcium in target organs could respond to the changes of calcium level, thus regulating calcium homeostasis. Also, a connection has been found between the CaSR gene A986S genotypes (986 Ala/Ser) and serum calcium concentrations within the normal range in healthy adult population.[4]

CA19-9 was discovered in the serum of patients with colon cancer and pancreatic cancer in 1981. It was characterized shortly and it was found to be carried primarily by mucins. Carbohydrate antigen 19-9 (CA19-9), also known as sialyl-Lewis A, is a tetra saccharide with the sequence Neu5Acα2-3Galβ1-3[Fucα1-4] GlcNAcβ, which is usually attached to O-glycan's on the surface of cells. It is known to play a vital role in cell-to-cell recognition processes. It is also a tumor marker and used primarily in the management of pancreatic cancer. CA19-9 can be elevated in many types of malignant and benign condition. It can also be elevated in people with obstruction of the bile ducts. In patients who lack the Lewis antigen (a blood type antigen on red blood cells), CA19-9 is not produced by any cells, even in those with large tumors. This is because of a deficiency of a fucosyl transferase enzyme that is needed to produce Lewis antigen A, that's why sometimes results are false positive and false negative.[5] Carcinoembryonic antigen(CEA) is the commonly used tumour marker in patients of colorectal carcinomaand CA19.9 might be used as an additional marker in patients of colorectal carcinoma.

II. Material and Methods

This was a hospital based observational study started from June 2019 to December 2020 or till the sample size was achieved at Department of General surgery, S.M.S. hospital, Jaipur, Rajasthan, India. The study included Sample size of 40 Patients whose detailed history and clinical examination was done. Sample size is calculated at 95% confidence interval and 0.05 alpha error assuming mean level of calcium 2.26, at expected SD of 0.17 as per seed article Relationship between serum calcium and CA 19-9 levels in colorectal cancer Peter Fuszek ET al.[7] All patients admitted in surgical OPD of S.M.S. Hospital with colorectal cancer, who went through inclusion and exclusion criteria.

Inclusion criteria: 1. Patients admitted in surgical department of S.M.S. Hospital Patients with histopathologically proven Colorectal cancer. 2. Patients who have given informed and written consent.

Exclusion criteria: 1. Associated with other malignancy and chronic Illness where CA 19-9 and serum calcium are deranged.

III. Observations and Results

Incidence of colorectal carcinoma in > 50 years of age is 47.5%. Incidence below 50 years age is 52.5%. 55.00% cases were male ,10% higher than females. 55.00% patients were smoker and 45.00% patients were non smoker. In our study, 42.50% patients present with obstruction, 32.50% patients present with per rectal bleed, 17.50% patients present with abdominal pain and lump, 5.00% patients present with abdominal pain and per rectal bleed, and 2.50% patients present with abdominal lump. So, the most common presentation of colorectal carcinoma cases in our study was intestinal obstruction.

Table 1: CA19.9 and serum calcium level relation with colorectal carcinoma stage
(AJCC TNM Staging System for colorectal carcinoma)

	No. of COLORECTAL CARCINOMAs Patients	CA 19.9		CALCIUM	
		Mean	SD	Mean	SD
Stage 2	10	101.34	236.52	8.08	0.82
Stage 3	23	31.33	21.51	8.19	0.59
Stage 4	7	230.67	429.61	7.25	0.49
P-value		0.097		0.005	

Table no. 1 shows that stage of colorectal carcinoma and CA 19.9 level had higher trends in stage IV but the p value couldn't come as significant. P value of relationship between stage IV colorectal carcinomaand calcium value did come out as significant in this study.

Table 2: CA 19.9 and serum Calcium relation

CA 19.9 Level	Calcium		No. of patients
	Mean	SD	
0-37 u/ml	8.21	0.75	23
>37 u/ml	7.72	0.52	17
p value	0.032		

Table 2. shows that serum calcium and CA 19.9 level are inversely related and this relationship is statistically significant.

Table 3 CEA and CA19.9

CEA level	No. of patients	CA 19.9	
		Mean	SD
>5 ng/ml	22	91.1	249.63
≤5 ng/ml	18	74.7	176.09
p value	0.815		

Table 3 shows that in our study mean CA19.9 level of patients with CEA >5ng/ml is 91.10±249.63 and mean CA19.9 level of patients with CEA< 5ng/ml is 74.70±176.09 with a p value of 0.815 which is not statistically significant.

Table 4- Percentage of patients with CEA and CA19.9

CEA	CA 19.9			
	0-37 ng/ml		>37ng/ml	
	No of Patients	Percentage	No of Patients	Percentage
>5ng/ml	13	32.5	9	22.5
≤5ng/ml	10	25	8	20

Table 4 shows that in our study with colorectal carcinomapatients, 32.5 % had only increased CEA levels, 22.5% had both CEA and CA19.9 levels raised, 25% had normal CEA and CA19.9 levels, 20 % had only CA19.9 levels raised.

In our study,23 patients had CA 19.9 <37u/ml. 13 patients had between 38-100 u/ml and 4 patients had >100u/ml.

In our study,mean serum calcium level was 8.00±0.71mg/dl.

In our study mean serum CEA level was 10.8±16.64.

In our study, 30 patients had serum calcium< 8.5mg/dl and 10 patients had between 8.5 – 10.5mg/dl. Mean serum calcium level in our study was 8.0mg/dl±0.71

Mean CA 19.9, 139.19±279.28 in< 30 years, mean CA 19.9, 56.35±42.60 in 31-40 years, mean CA 19.9, 18.74±12.71 in 41-50 years, mean CA 19.9, 215.20±435.24 in 51-60 years, 29.86±41.55 in 61-70 years and 45.22±26.68 in 71-80 years.

Preoperative values of parameters were as follows: mean Serum CA 19.9 level was 83.71±217.11,mean calcium level was 8.00±0.716, mean CEA level was 10.8±16.64, mean albumin level was 3.35±0.43, mean vitamin D level was 24.48±5.77, mean serum phosphorus level was 3.62±0.52.

Thus, only mean calcium level was found to be mildly below normal limits in patients of colorectal carcinoma.

IV. Discussion

Colorectal cancer incidence, prevalence, and mortality are increasingly becoming a global burden. It was before 1900 a rare disease in the western population but has become a common disease and continue to increasing yearly in that region of the world. Colorectal cancer incidence, prevalence, and mortality are

increasing. In this study we analyzed the correlation between tumor markers and different clinicopathological features of colorectal carcinoma and compare of mean level of these markers in colorectal carcinoma cases.

Stage of the Disease: In our study maximum number of patients presented with stage 3 (n=23) (57.5%), rest were stage 2(n=10) (25%) and stage 4 (n=7) (17.5%). Mark B Ulanza et al[6] found 24.1% stage 1, 27.3% stage 2 , 28.2% stage 3 and 20.4% stage 4 disease. Maximum number of patients in their study were in stage 3 at the time of presentation. They also found right sided cancers more likely T4. The late presentation of colorectal carcinoma can be attributed to lack of awareness in India, so screening awareness is required.

In our study, 17 patients with CA19.9 level >37U/ml had mean calcium value 7.72 mg/dland 23 patients with CA19.9 level <37 U/ml had mean calcium value 8.21mg/dl . shows that serum calcium and CA 19.9 level are inversely related and this relationship is statistically significant.

Recently Wulaningsih et al had noted a similar finding to that of Fuszek et al in their own study.[7] These reports by Fuszek et al and Wulaningsih et al[8] are all in accord with this study where we noted a low calcium level more pronounced among those with positive higher value of CA19.9 levels. However, Fuszek et al[7] had reported a null relationship (p=0.79) between Serum Calcium and CA19.9 level in their study. In comparison with this, we observed a significant inverse association between serum Calcium and CA19.9 level , 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 our study. The mechanism of calcium protective effects in colorectal carcinogenesis is ill-understood. However, several mechanisms have been suggested and reported by several authors.

In our study with colorectal carcinoma patients, increase in only CEA levels with normal CA19.9 levels found in 32.5%, both CEA and CA19.9 levels raised in 22.5%, normal CEA and CA19.9 levels in 25% and only CA19.9 levels raised with normal CEA levels in 20% .So in our study CA19.9 raised in 42.5% of patients with colorectal carcinoma and CEA raised in 55% patients

In our study with colorectal carcinoma patients mean CA19.9 level with CEA >5ng/ml is 91.10±249.63 and mean CA19.9 level of patients with CEA<5ng/ml 74.70±176.09 with a p value of 0.815 which is not statistically significant. Stiksma J et al[9] (2014) 56 conducted a study on patients with histologically confirmed colorectal cancer. In patients with colorectal cancer and 3 serial measurements of tumor markers, 7.3% had only increased CA 19-9 levels without increased CEA levels, and 55.4% of the patients had an increase of CA 19-9 and CEA levels. In the patients with available preoperative markers, patients with only an increase of CA 19-9 had a significantly decreased 5-year survival compared with patients with an increase of only CEA (P = .013).CA 19-9 can be used as additional marker to follow the disease process in patients with colorectal cancer without an increase in CEA level. Patients with preoperative increased CA 19-9 level had a poorer 5-year survival than patients with preoperative increased CEA levels.

In our study, out of 40 colorectal carcinomapatients ,30 of them with normal mean serum vitamin D level 24.48±5.77 ng/ml, had serum calcium <8.5mg/dl with p value of less than 0.001, which is statistically significant .So our study indicates colorectal carcinomas are associated with low serum calcium values.

The role of calcium as a nutritional and dietary risk factor in colorectal carcinogenesis has been well-documented in the literature.[10-11] Wichendu PN et al[12] reported rate of hypocalcemia in their patients is higher than the 11.53% prevalence rate of hypocalcemia reported among Nigerian patients attending a tertiary hospital reported 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.[13,14] This finding supports the numerous epidemiologic reports of the involvement of low plasma calcium in colorectal carcinogenesis.

In our study mean CA 19.9 and mean Calcium with mean vitamin D level 24.48±5.77 ng/ml, in stage 2, 3 & 4 are (101.34,8.08), (31.33,8.19) & (230.67,7.25) respectively. It shows that stage 4 disease has higher CA 19.9 and low serum Calcium and associated with poor prognosis. A study by Wang WS et al (nov 2000)[11] indicate that serum CA19-9 level significantly rise in metastatic colorectal carcinomaand is prognostic indicator of patients with metastasis.

In our study, Mean albumin level was 3.35±0.43, Mean vitamin D level was 24.48±5.77 and Mean Serum phosphorus level was 3.62±0.52. So in this study Serum phosphate and serum albumin levels are in the lower end of the normal range . There was no deviation in mean Serum vitamin D level in Colorectal carcinoma cases and was found to be in normal range. In a study by Peter Fuszek et al[7] (nov. 2004) came to similar conclusion ,as they found serum albumin and Serum phosphorus levels to be in the lower limits of its range.

V. Conclusion

As we found association between colorectal cancer cases and serum calcium level with normal mean serum vitamin D level, was statistically significant and association between serum calcium and serum CA 19.9 level was also statistically significant and inversely related . Elevated serum CA19.9 levels were associated with the higher staged disease or the presence of metastasis. So we conclude that CA19.9 tumour marker had a

prognostic role in colorectal carcinoma. It supports the significance of serum calcium not only as a pathogenic factor but also as a prognostic factor. So by increasing calcium intake, the multileveled pathogenic process leading to tumorigenesis might be influenced but it requires further research and randomized controlled multicentric trials.

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