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Regular Article

Association between Tumor Markers and Macro Metals – Calcium and Magnesium

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Abstract

Monoclonal antibodies are used to detect serum antigens associated with malignancies. The tumor markers are most useful for monitoring response to therapy and detecting early relapse. Tumor markers are special molecules released by tumor cells, found in high levels in patients with malignancies. Each tumor marker is organ specific and is elevated in specific type of malignancy and its level in circulating blood provide a clue about the type and severity of the disease. The blood level is very useful for diagnosis, prognosis and to check recurrence after treatment. Experiments were performed to investigate and establish if there are any associations between the principle tumor markers viz CEA (colon caner) , CA125 (ovarian cancer) and CA15.3 (breast cancer) to the diagnostically useful macro-metals Calcium and Magnesium and to suggest if the above two metals need to be analyzed along with the tumor markers for the diagnostic purposes. The study was done with the blood serum sample of suspected or established cancer patients (both men and women). For the samples, biochemical assay using electro-chemiluminescence technique (for CEA, CA 125 and CA 15.3) was used; Calcium and Magnesium were analyzed using manual dye-binding methods and the readings were acquired using a semi auto analyzer. Appropriate statistical methods were used to conclude that, there exists a very strong relationship between CA 125 and CA 15.3; and proved that CA 15.3 is linked to both metals Calcium and Magnesium; whereas CEA shows an inverse correlation with CA 125.

Introduction

In recent years, laboratory diagnosis has achieved a prominent place in medical services and hence lab services form an integral part of the health care delivery.

In this study, an attempt has been made to investigate and establish if there are any associations between the principle tumour markers viz., CEA, CA125 and CA15.3 to the diagnostically useful macro-metals Calcium and Magnesium and to suggest if the above two metals need to be analyzed along with the tumor markers for the diagnostic purposes.

Review

Monoclonal antibodies are used to detect serum antigens associated with malignancies. The tumor markers are most useful for monitoring response to therapy and detecting early relapse.
Tumor markers are special molecules released by tumor cells; found in high levels in patients with malignancies. Each tumor marker is organ specific and is elevated in specific type of malignancy and its level in circulating blood provide a clue about the type and severity of the disease. The blood level is very useful for diagnosis, prognosis and to check recurrence after treatment. For example prostrate specific antigen (PSA) is a very specific and useful screening test for prostrate cancer and to monitor the response to treatment. The blood level correlates well with Digital Rectal Examination (DRE).
The ideal marker for the purpose of diagnosis would have two characteristics: 1) it would be secreted into the blood in measurable concentration only after the cells that produced it has undergone malignant transformation and 2) detection of it would permit conclusion as to the site of tumor from which it arose. The use of diagnostic tests in the clinical setting is highly controlled by regulatory bodies, but Tumor Markers have been particularly identified for special consideration.

Carcinoembryonic antigen (Cea)

CEA, an oncofetal glycoprotein, is expressed in normal mucosal cells and over expressed in adeno carcinoma, especially colorectal cancer. CEA elevation also occurs with other malignancies. CEA is not useful in the screening of colorectal cancer. This test should be ordered only after malignancy has been confirmed. CEA levels typically return to normal within 4 to 6 weeks after successful surgical resection.

Cancer antigen 125 (CA 125)

CA125 is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelopes the ovaries.Elevated CA125 values most often are associated with epithelial ovarian, although levels also can be decreased in other malignancies. CA125 levels are elevated in about 85% of women with ovarian cancer, but in only 50% of those with stage 1 disease. Multiple benign disorders also are associated with CA125 elevations, presumably by stimulation of the serosal surfaces.

Cancer antigen 15.3 (CA 15.3)

CA 15-3 is a high molecular weight (300 to 450 kDa) polymorphic epithelial mucin, also known as breast cancer mucin, that is produced by many cancers of the breast. It is not used for screening, but is recommended as a follow up after breast cancer has been treated. In some cases it will allow a relapse to be detected before becoming clinically apparent. CA15-3 is not elevated during pregnancy. The percentage of raised values found in breast cancer can be as high as 98%, but this depends primarily on the tumor stage of the patient population studied. Elevated levels have also been found in patients with lung cancer (63%) and ovarian cancer (80%).

Calcium and cancer

Experts say excessive calcium intake may be unwise in light of recent studies showing that high amounts of the mineral may increase risk of prostate cancer. "There is reasonable evidence to suggest that calcium may play an important role in the development of prostate cancer," says Dr. Carmen Rodriguez, senior epidemiologist in the epidemiology and surveillance research department of the American Cancer Society (ACS).

The adverse effects of excessive calcium intake may include high blood calcium levels, kidney stone formation and kidney complications. Elevated calcium levels are also associated with arthritic/joint and vascular degeneration, calcification of soft tissue, hypertension and stroke, and increase in VLDL triglycerides, gastrointestinal disturbances, mood and depressive disorders, chronic fatigue, and general mineral imbalances including magnesium, zinc, iron and phosphorus. High calcium levels interfere with Vitamin D and subsequently inhibit the vitamin's cancer protective effect unless extra amounts of Vitamin D are supplemented.

Magnesium and cancer

One of the first organs to calcify is the ovaries leading to pre-menstrual syndrome. High magnesium diet has reversed the above

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status. There is no substitute for magnesium in human physiology; nothing comes even close to it in terms of its effect on overall cell physiology. Without sufficient magnesium, the body accumulates toxins and acid residues, degenerates rapidly, and ages prematurely. It goes against a gale wind of medical science to ignore magnesium chloride used transdermally in the treatment of any chronic or acute disorder, especially cancer. Early signs of magnesium deficiency are, loss of appetite, nausea, vomiting, fatigue and weakness. Increased deficiency may show as numbness, fingling, muscle contractions and cramps, seizures, personality change, abnormal heart rhythms and coronary spasms. Severe deficiency results with hypocalcemia and hypokalemia.Magnesium have a calming effect on the nervous system and are frequently used to promote good sleep. It can be used to calm irritated and over excited nerves. Epilepsy is marked by abnormally low levels of magnesium in blood.

Materials and Method

After completely going through the literature review where Calcium and Magnesium, are cited either as causative factor in inducing cancer of a particular type by its deficiency or accumulation, we decided to select a reasonable number (n=64) of suspected or established cancer patients to evaluate if any association exist between the type of cancer and the individual metals.

Subjects

64 patients comprising of both male and female in the age group of 14 to 79 who reported to the out patient clinic for cancer related symptoms (routine screening as well as established cancer patients) were enrolled for the study. As the laboratory has recently established normal values for 3 tumor markers and 2 metals for which we wanted to evaluate association, we directly estimated those parameters for the purpose of finding an association. The subjects selected consisted of 39 females in the age group of 14 to 71 years and 25 males in the age group of 24 to 79 years. In order to cover our study for a wide range of age and sex related subjects.

Sample collection

As tumor markers and metals do not vary due to fasting or non-fasting status, sample collection was done between 9-10.30 am for all the patients. Exact sample collection procedures were followed, such as use of sterile and disposable needles and vaccutainer for collecting the samples. Qualified phlebotomist was used in all blood collection in order to prevent pre-analytical errors that may be carried to the assay stage. This includes a correct site of vein puncture and the pressure used to transfer the blood into the vaccutainer.

Sample processing

All the blood samples were allowed to clot at room temperature for 30 minutes, the tubes were gently tapped to displace clot adhering to the tube and then centrifuged with the cap on in each tube for 10 minutes at 2500 rpm. Serum from each tube was transferred to another set of appropriate labeled tubes using disposable plastic dropping pipettes. The samples were either analyzed immediately or preserved at 2-8°C if there is a delay in analysis.

Biochemical assays

Using the latest electro-chemiluminiscent analyzer, (Updated version of Enzyme Immuno Assay), used for the assay of Hormones, Tumor Markers and Drugs, 3 tumor markers (CEA, CA 125 and CA 15.3) were estimated. Extensive quality control measures were done so as to get accurate values.

For measuring Calcium and Magnesium, manual dye-binding methods were used and the readings were acquired using a semi auto analyzer.

Results and Discussion

Table 1 shows the results obtained for all the patients, for the 3 tumor markers and 2 metals (Calcium and Magnesium) along with their ratio. As CA 125 and CA 15.3 refers only to the female patients, it is hence not presented for the male patients. The mean and the Standard Deviation for the same are given in this table along with its normal range.

It is clearly seen from the Table that, the mean values for the tests CA125 and CA 15.3 are highly elevated. This is due to the fact that, a few patients had values in the abnormal range, which contributed for the higher Mean and Standard Deviation. CA 15.3 too is on the upper limit, while, Calcium mean value is on the lower limit of the normal range and Magnesium is on the median level.

We neither have selected a separate control group, nor chose established cancer patients, but have randomly selected, patients who attended the Cancer Screening Program, at our Oncology Department.
From the individual values obtained, we can see that, the majority of the patient values are within the normal range.

Since the sole aim of the study was to establish a relationship between the 3 tumor markers namely (CEA, CA125 and CA15.3), and the macro-metals (Calcium and Magnesium), we have presented all the data together in a single Table.

As the mean age of all the patients is 54, the age at which many people attend the cancer screening program, justifies that our study was done using patients attending cancer program.

Since CA 125 and CA 15.3 are tumor markers related to females, the same was not carried out for the male population. Table 2 presents similar data for 39 females out of 64 total patients. Just like Table 1, the mean age for female patients is calculated to be 53. CA 125 and CA 15.3 were analyzed for all 39 patients whereas CEA was done for 27 patients. The CEA analysis was stopped with 27 in Table 2 since the total CEA samples analyzed exceeded the initial plan of 50 (Total CEA analyzed was 52). The mean values in Table 2, for the markers CEA and CA125, are very high because, a few patient samples recorded abnormal values. The mean value of CA 15.3 is close to the upper limit. As observed in Table 1, mean Calcium is at the lower limit and mean Magnesium is at the median range. Table 3 represents data for CEA, Calcium, Magnesium, and the ratio between Calcium and Magnesium for 25 Male patients. Here, the mean Age is similar to that in Table 1 and 2. Mean CEA was found to be twice the Upper Limit and both Calcium and Magnesium are close to the normal range. Since the mean Calcium and Magnesium values are similar to the values followed in the Clinical Laboratory, we envisage that there may not be any significant correlation if subjected to statistical analysis.

Table 1 – All patients

S.no	Age	Sex	CEA	CA 125	CA 15.3	Ca	Mg	Ca/Mg
1	50	F	3.7	7927	93.7	9	2.21	4.07
2	59	M	1.7			9.4	1.85	5.08
3	64	M	2.3			9.6	1.94	4.94
4	55	M	5.1			9.4	1.94	4.84
5	54	F	1.1	65.3	37.56	9.8	1.82	5.38
6	57	M	1.9			9.5	1.86	5.1

7	79	M	3.2			9.5	2.06	4.61
8	74	M	2.6			10.3	1.79	5.75
9	24	M	4.8			9.4	2.26	4.15
10	66	M	1			9.3	2.2	4.22
11	45	F	0.7	119	8.1	7.3	2.23	3.27
12	49	F	105	25	18.92	9.4	1.87	5.52
13	74	M	7			11	2.06	5.33
14	56	M	58			9.4	1.9	4.94
15	54	M	1			9.5	1.78	5.33
16	60	M	2.9			13.1	2.02	6.48
17	71	F	3.3	8	15.72	9.3	2.6	3.57
18	48	M	6.1			8.7	1.78	4.88
19	43	F	3.76	19.92	14.35	9.3	2.08	4.47
20	53	M	4.2			8.7	2.1	4.14
21	75	M	11.2			9.7	1.65	5.87
22	32	F	1.53	40.7	11.18	8.9	1.67	5.32
23	60	M	2.5			8.9	1.91	4.65
24	56	M	2.6			9.6	2.5	3.84
25	48	F	4.42	13.83	14.91	8.8	2.03	4.33
26	50	M	4.7			8.8	2.22	3.96
27	14	F	1.22	15.44	9.27	9.1	1.92	4.73
28	48	F	2.09	14.23	11.95	8.9	1.61	5.52
29	65	F	167.5	1.09	10.4	9.3	1.87	4.97
30	68	F	0.775	35.04	6.7	8.7	2.1	4.14
31	63	F	6.11	14	29	8.1	2.09	3.87
32	46	F	0.6	38	19	8.6	2.3	3.73
33	65	F	2	6.56	11	8.6	1.78	4.83
34	67	F	2	456.7	17	7.9	1.84	4.29
35	56	F	1.96	1078	86	7	2.52	2.77
36	66	F	3	19	9	8.7	1.93	4.5
37	60	M	1.9			8.8	2.48	3.54
38	50	F	1.9	6	21.57	9.7	1.68	6.06
39	57	M	8			10.4	1.8	5.77
40	43	F	2.36	10	12.31	9.5	1.88	5.05
41	47	M	3			9.5	1.73	5.49
42	41	M	1.8			10.1	1.81	5.58
43	47	F	3.88	13.48	24.31	9.6	2.01	4.77
44	60	F	1.76	7	13.88	9	1.44	6.25
45	29	M	0.2			10	2.29	4.36
46	57	M	14			9.6	1.95	4.92
47	58	F	0.5	6	12.9	9.1	1.7	5.35
48	53	M	11.1			8.1	1.93	4.19
49	63	F	1.8	8.32	21.99	8.5	1.66	5.12
50	55	F	65	114.7	79.42	8.4	2.11	3.98
51	54	F	3	9	17.48	9.7	2.14	4.53
52	62	F	14.4	22.77	24.04	10.1	2	5.05
53	52	F		249	84	7.2	1.72	4.18
54	60	F		348.4	19	9.5	1.44	6.59
55	52	F		16	23	9.7	1.66	5.84
56	40	F		16	13	9.6	1.77	5.42
57	69	F		1106	77	9.2	1.913	4.8
58	43	F		63	31	8.7	1.7	5.11

59	46	F		11	21	10.1	1.92	5.26
60	57	F		82.5	31	8,6	2.25	3.82
61	44	F		103	46	9.4	1.61	5.83
62	71	F		6	21	8.8	1.92	4.58
63	52	F		15.7	8.3	9.6	1.52	6.31
64	40	F		29	14.2	10.3	2.16	4.76

	Age	**CEA**	**CA 125**	**CA 15.3**	**Ca**	**Mg**	**Ca/Mg**
Mean	54.32	10.92	311.27	26.67	9.24	1.94	4.84
Standard Deviation	12.14	28.55	1276.28	23.85	0.88	0.26	0.8
Normal Range		<3.0	<35	<40	8.4 – 10.2	1.6 – 2.3	

Table 2- Female patients

S.no	**Age**	**Sex**	**CEA**	**CA 125**	**CA 15.3**	**Ca**	**Mg**	**Ca/Mg**
1	50	F	3.7	7927	93.7	9	2.21	4.07
2	54	F	1.1	65.3	37.56	9.8	1.82	5.38
3	45	F	0.7	119	8.1	7.3	2.23	3.27
4	49	F	105	25	18.92	9.4	1.87	5.52
5	71	F	3.3	8	15.72	9.3	2.6	3.57
6	43	F	3.76	19.92	14.35	9.3	2.08	4.47
7	32	F	1.53	40.7	11.18	8.9	1.67	5.32
8	48	F	4.42	13.83	14.91	8.8	2.03	4.33
9	14	F	1.22	15.44	9.27	9.1	1.92	4.73
10	48	F	2.09	14.23	11.95	8.9	1.61	5.52
11	65	F	167.5	1.09	10.4	9.3	1.87	4.97
12	68	F	0.775	35.04	6.7	8.7	2.1	4.14
13	63	F	6.11	14	29	8.1	2.09	3.87
14	46	F	0.6	38	19	8.6	2.3	3.73
15	65	F	2	6.56	11	8.6	1.78	4.83
16	67	F	2	456.7	17	7.9	1.84	4.29
17	56	F	1.96	1078	86	7	2.52	2.77
18	66	F	3	19	9	8.7	1.93	4.5
19	50	F	1.9	6	21.57	9.7	1.68	6.06
20	43	F	2.36	10	12.31	9.5	1.88	5.05
21	47	F	3.88	13.48	24.31	9.6	2.01	4.77
22	60	F	1.76	7	13.88	9	1.44	6.25
23	58	F	0.5	6	12.9	9.1	1.7	5.35
24	63	F	1.8	8.32	21.99	8.5	1.66	5.12
25	55	F	65	114.7	79.42	8.4	2.11	3.98
26	54	F	3	9	17.48	9.7	2.14	4.53
27	62	F	14.4	22.77	24.04	10.1	2	5.05
28	52	F		249	84	7.2	1.72	4.18
29	60	F		348.4	19	9.5	1.44	6.59
30	52	F		16	23	9.7	1.66	5.84
31	40	F		16	13	9.6	1.77	5.42
32	69	F		1106	77	9.2	1.913	4.8
33	43	F		63	31	8.7	1.7	5.11
34	46	F		11	21	10.1	1.92	5.26
35	57	F		82.5	31	8,6	2.25	3.82

•	• **Age**	• **CEA**	• **Ca**	• **Mg**	• **Ca/Mg**
• Mean	• 56.32	• 6.51	• 9.61	• 1.99	• 4.87
• Standard Deviation	• 12.81	• 11.28	• 0.95	• 0.22	• 0.71

36	44	F		103	46	9.4	1.61	5.83
37	71	F		6	21	8.8	1.92	4.58
38	52	F		15.7		9.6	1.52	6.31
39	40	F		29		10.3	2.16	4.76

Table 3 - Male patients

	Age	**CEA**	**CA125**	**CA15.3**	**Ca**	**Mg**	**Ca/Mg**
• **S. no.**	• **Age**	• **Sex**	• **CEA**	• **Ca**	• **Mg**	• **Ca/ Mg**	
• 1	• 59	• M	• 1.7	• 9.4	• 1.85	• 5.08	
• 2	• 64	• M	• 2.3	• 9.6	• 1.94	• 4.94	
• 3	• 55	• M	• 5.1	• 9.4	• 1.94	• 4.84	
• 4	• 57	• M	• 1.9	• 9.5	• 1.86	• 5.1	
• 5	• 79	• M	• 3.2	• 9.5	• 2.06	• 4.61	
• 6	• 74	• M	• 2.6	• 10.3	• 1.79	• 5.75	
• 7	• 24	• M	• 4.8	• 9.4	• 2.26	• 4.15	
• 8	• 66	• M	• 1	• 9.3	• 2.2	• 4.22	
• 9	• 74	• M	• 7	• 11	• 2.06	• 5.33	
• 10	• 56	• M	• 58	• 9.4	• 1.9	• 4.94	
• 11	• 54	• M	• 1	• 9.5	• 1.78	• 5.33	
• 12	• 60	• M	• 2.9	• 13.1	• 2.02	• 6.48	
• 13	• 48	• M	• 6.1	• 8.7	• 1.78	• 4.88	
• 14	• 53	• M	• 4.2	• 8.7	• 2.1	• 4.14	
• 15	• 75	• M	• 11.2	• 9.7	• 1.65	• 5.87	
• 16	• 60	• M	• 2.5	• 8.9	• 1.91	• 4.65	
• 17	• 56	• M	• 2.6	• 9.6	• 2.5	• 3.84	
• 18	• 50	• M	• 4.7	• 8.8	• 2.22	• 3.96	
• 19	• 60	• M	• 1.9	• 8.8	• 2.48	• 3.54	
• 20	• 57	• M	• 8	• 10.4	• 1.8	• 5.77	
• 21	• 47	• M	• 3	• 9.5	• 1.73	• 5.49	
• 22	• 41	• M	• 1.8	• 10.1	• 1.81	• 5.58	
• 23	• 29	• M	• 0.2	• 10	• 2.29	• 4.36	
• 24	• 57	• M	• 14	• 9.6	• 1.95	• 4.92	
• 25	• 53	• M	• 11.1	• 8.1	• 1.93	• 4.19	
Mean	53.026	15.014	311.27	26.671	9.0105	1.9147	4.819
Standard Deviation	11.679	38.026	1276.3	23.852	0.7693	0.2705	0.858
Normal Range		<3.0	<35	<40	8.4-10.2	1.6-2.3	

• Normal Range	•	• <3.0	• 8.4 – 10.2	• 1.6 – 2.3	•

Table 4- All patients

S.no	Pairs compared	R	t	p
1	CEA Vs CA 125	-0.35924	-2.34	0.0124
2	CA 125 Vs Mg	0.21261	1.32	0.0969
3	CA 125 Vs CA 15.3	0.57099	4.23	<.0001
4	CA 15.3 Vs Ca	-0.35924	-2.34	0.0124
5	CA 15.3 Mg	0.21262	1.32	0.0969
6	CA 15.3 Vs Ca/ Mg Ratio	-0.335	2.16	0.0185

Table 5- Female patients

S.no	Pairs compared	R	t	p
1	CA 125 Vs Mg	0.21262	1.32	0.0969
2	CA 125 Vs CA 15.3	0.57099	4.23	<.0001
3	CA 15.3 Vs Ca	-0.35924	-2.34	0.0124
4	CA 15.3 Mg	0.21262	1.32	0.0969
5	CA 15.3 Vs Ca/ Mg Ratio	-0.335	2.16	0.0185

Statistical analysis of data

Table 4 gives the statistical parameters ie, Correlation co-efficient (r), Students Distribution (t) and probability (p), for the three tumor markers compared in pairs. Only CA 125 and CA 15.3 comparison to the metals and the ratio of the metals are presented in this Table, since no correlation was obtained when compared CEA with either Calcium or Magnesium.It is interesting to observe from this table that, there is a strong relationship between CA 125 and CA 15.3 (r= 0.57099; t= 4.23; p= <0.001), suggesting that, while screening for tumors in female in one organ, it is important to estimate the markers for the other. CA 15.3 shows inverse correlation to both Calcium and the ratio between Calcium and Magnesium (P= >0.05), thereby linking CA 15.3 to both metals. As CA 125 and CA 15.3 shows excellent correlation, CA 125 too must be associated with Magnesium. One interesting observation is that, while CEA as presented in Table 3, did not show any correlation to any of the metals, it gives an inverse correlation with CA 125. As CA 125 is correlated to both metals, CEA too should have an association to the metals thereby linking all the three tumor markers to the macro metals. Table 5 presents similar data to that of Table 4, except that, it is for female patients. This table does not contain CEA contrary to the one seen in Table 4. This suggests that the circulating levels in female patients may not have association to the Metals. The statistical parameters (r; t; and p) obtained for female group is almost similar to the one in Table 4. Hence the outcome is almost as described for Table 4.

Conclusion

Previous studies have established the importance of both Calcium and Magnesium in almost all types of Cancer. Both Hypocalcemia and Hypomagnesemia, were observed in critically ill cancer patients and Magnesium deficiency can directly lead to Cancer. Our study although did not establish the above statements, we have found out the association between the tumor markers present in a specific cancer and the metals Calcium and Magnesium. Since the population selected were from Oncology Clinic, the mean values for Calcium and Magnesium were at the lower end while, the tumour marker values were at the higher end. This suggests that, in established Cancer patients, the two metal concentrations may be lower as found in majority of the previous studies. Many western studies, unlike the Indian literature, have many data, linking Cancer Antigens to Metals. It is time that the medical profession start using Magnesium as a primary treatment tool, since it is very difficult to find cancer patients with normal levels of Calcium and Magnesium. Our findings too are consistent with the pervious observations. A recent article on Cancer and Magnesium predict that 46% of all Cancer patients admitted to ICU were presented with Hypocalcaemia and Hypomagnesaemia and our study partially established this observation. As the number of male patients are only 25, were unable to establish a direct relationship between CEA and the metals, but its relationship with metals were linked by CA 125, thereby bringing into the picture, the association between CEA and the metals.

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