

SERUM COPPER LEVEL IN FEMALE GENITAL MALIGNANCIES AND DYSPLASIA

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SUMMARY

Serum copper levels (SCL) were determined in 65 women with various histologically proven gynaecologic cancers and 25 patients with varying degrees of cervical dysplasia. SCL was significantly higher ($p < 0.01$) in all groups of patients with cancer and with dysplasia when compared with control subjects. A good correlation was established between SCL and the degree of dysplasia and the stage of malignant disease. After successful treatment, SCL was observed to fall ($p < 0.01$) to near normal levels irrespective of the mode of therapy. These results indicate that SCL can be used as a valuable biochemical index for evaluating the disease process and management of premalignant and malignant gynaecologic lesions.

Introduction

The last decade has been a major effort to identify tumour markers by simple, reliable laboratory methods. The serum copper level has been the subject of a multitude of investigations in non-neoplastic and neoplastic conditions. High serum copper levels were found in malignant lymphoproliferative disorders and several other malignancies (Schwartz, 1975). It was established that serum copper levels are of considerable importance in assessing disease activity, response to treatment and recurrence of tumour in cancer patients.

Among gynaecology malignancies,

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serum copper levels have been suggested as being of great interest in evaluating the extension and clinical evolution of the disease (O'Leary and Feldman 1970; Margalioth et al, 1987).

The present study has been undertaken to assess the changes in SCL in various pre-malignant and malignant conditions of the female genital tract in order to evaluate its use as a diagnostic and prognostic index.

Material and Methods

The present study was undertaken in the Patna Medical College, Patna, during the period 1987-89. A total of 120 cases were studied. 30 women of reproductive age-group free from gynaecological and medical diseases and not taking hormones

were studied as healthy controls. 25 women were those suffering from cervical dysplasia and 65 patients were those with gynaecological malignancies.

After careful history taking, complete clinical examination was carried out in every case. Routine and special investigations were performed in all cases. Patients known to have liver disease or those receiving hormones were excluded from the study. The final diagnosis was based on histologic proof in all cases. Staging of malignancy was assigned according to the FIGO classification system. Cases of cervical dysplasia were classified into CIN grades I, II and III.

The patients were subjected to various modalities of treatment, viz. surgery, radiotherapy, chemotherapy or a combination of these methods. The pre-treatment and post-treatment serum copper levels were estimated in each case by the Diethyldithiocarbamate method (Varley et al 1980).

- (i) before the start of specific therapy; and
- (ii) at the end of specific therapy-either at the time of discharge, or a month after treatment.

Observations

Of the 65 patients with gynaecologic malignancies, 46 had carcinoma cervix, 6 had carcinoma endometrium, 8 had carcinoma ovary, 3 had choriocarcinoma and 2 had carcinoma vulva. 13 patients with cervical dysplasia had CIN-I lesion, 8 had CIN-II and 4 had CIN-III lesion. Most patients with cervical dysplasia were in the age range of 31-40 years, while those in malignant group mostly belonged to 41-50 years age-group. Multiparous patients predominated in patients with dysplasia and malignant lesions and most patients belonged to the low socio-economic group.

Serum copper levels in healthy controls ranged from 78-135 $\mu\text{g}/100\text{ ml}$ with a mean of $103.43 \pm 19.39\ \mu\text{g}\%$. Table I summarises the number of patients in each group with the corresponding serum copper level. The pre-treatment serum copper level was significantly higher ($p < 0.01$) in all groups of opatients with cancer and with cervical dysplasia when compared with the control group. The serum copper level rose progressively with increasing grades of dysplasia (Table II). After treatment a significant fall ($p < 0.01$) in serum copper level was noted in all patients irrespective of the grade.

TABLE - I
SHOWING SERUM COPPER LEVELS IN CONTROLS,
DYSPLASIA AND MALIGNANT LESIONS

Groups	No.	SCL ($\mu\text{g}/100\text{ ml}$)		t	p
		Range	Mean \pm S.D.		
Control	30	78-135	103.43 ± 19.39	—	—
Dysplasia	25	119-152	133.32 ± 8.07	3.92	<0.01
Malignancy :					
Ca.cervix	46	127-202	160.74 ± 8.89	96.21	<0.01
Ca.endo.	6	139-185	155.50 ± 26.77	45.83	<0.01
Ca.ovary	8	179-217	193.88 ± 13.16	59.50	<0.01
Chorio ca.	3	183-248	211.00 ± 33.41	25.99	<0.01
Ca.vulva	2	148-181	164.50 ± 23.33	2.04	<0.05

TABLE - II
SHOWING SERUM COPPER LEVELS IN RELATION TO GRADES OF
DYSPLASIA AND THE EFFECT OF TREATMENT

Grade	No.	SCL (mean ± S.D. µg%)		Mean decrease in SCL	t	p
		Pre-treatment	Post-treatment			
CIN - I	13	131.38 ± 7.24	122.14 ± 5.13	11.28 ± 2.87	10.3	<0.01
CIN - II	8	133.88 ± 7.80	122.25 ± 7.59	11.63 ± 2.78	11.8	<0.01
CIN - III	4	143.75 ± 5.21	126.50 ± 7.35	17.25 ± 3.70	9.3	<0.01

A trend for progressive increase in serum copper level was observed with the advancement of staging in genital malignancies (Table III). Following successful therapy, serum copper level was observed to fall irrespective of clinical stages (Table IV), the fall being more significant in the earlier stages (P<0.01 in stages I, II and III, and <0.05 in stage IV). All cases, except one of choriocarcinoma of uterus who expired, showed a favourable response to

treatment with lowering of serum copper level.

Serum copper levels showed a significant increase with the degree of differentiation and histologic pattern of genital malignancies (Table V). Post-treatment values showed a significant fall which was more in the well differentiated group in comparison to the more undifferentiated tumours.

TABLE - III
SHOWING SERUM COPPER LEVELS IN MALIGNANT
LESIONS ACCORDING TO STAGE OF DISEASE.

Malignant lesion	No.	SCL (Mean ± S.D. µg%)			
		Stage-I	Stage-II	Stage-III	Stage-IV
Ca.cervix	46	146.66 ± 5.31	156.50 ± 14.32	163.44 ± 16.94	183.5 ± 18.5
Ca.endo	6	141.33 ± 2.05	163.00 ± 4.00	185	—
Ca.ovary	8	—	190	186.80 ± 5.52	213.5 ± 3.5
Ca.vulva	2	148	—	181	—

TABLE - IV
SHOWING SERUM COPPER LEVELS IN RELATION TO CLINICAL
STAGES OF CARCINOMA CERVIX AND THE EFFECT OF TREATMENT.

Clinical p	No.	SCL (Mean ± S.D. µg%)		Mean decrease in SCL	t	p
		Pre-treatment	Post-treatment			
3	145.66 ± 5.31	117.66 ± 10.96	28.00 ± 2.98	22.9	<0.01	
16	156.50 ± 14.32	128.06 ± 11.56	27.81 ± 6.26	17.8	<0.01	
25	163.44 ± 16.94	131.68 ± 10.74	31.76 ± 10.95	14.5	<0.01	
2	183.50 ± 18.50	145.50 ± 13.50	38.00 ± 3.15	12.7	<0.05	

TABLE - V
SHOWING SERUM COPPER LEVELS IN RELATION TO HISTOLOGICAL GRADE OF
CARCINOMA CERVIX AND THE EFFECT OF TREATMENT

Histological stage	No.	SCL (Mean \pm S.D. $\mu\text{g}\%$)		Mean decrease in SCL	t	p
		Pre-treatment	Post-treatment			
I	23	147.39 \pm 8.29	121.21 \pm 7.96	26.61 \pm 6.12	40.8	<0.01
II	15	167.20 \pm 7.87	133.60 \pm 5.82	33.60 \pm 7.96	11.4	<0.01
III	8	198.25 \pm 17.53	150.50 \pm 14.79	35.25 \pm 7.96	12.6	<0.01

Discussion

The importance of early diagnosis of cancer in monitoring disease activity, assessment of response towards therapy and timely detection of possible relapse cannot be over emphasised. Previous studies have demonstrated elevated serum copper levels in various malignancies and have suggested serum copper to be a promising tool in the diagnosis and monitoring of disease activity (Schwartz, 1975). In the present study, the average serum copper level in healthy controls was found to be $103.43 \pm 19.39 \mu\text{g}\%$ which was in consonance with those reported by other workers (Bhardwaj et al 1980; Birdi et al 1983).

Significantly elevated ($p < 0.01$) levels of serum copper were demonstrated in this study in patients with cervical dysplasia and gynaecologic cancers, the highest levels being observed in patients with chorio-carcinoma. The levels also correlated well with the clinical progression of the disease, showing a significant consistent rise with increasing dysplasia of cervix and in successive clinical stages of malignant disease. A rising trend was also evident when cases were split according to the degree of differentiation of the tumour.

The serum copper declined to normal values after successful surgery in patients with dysplasia. A significant post-treat-

ment decrease in serum copper values was also observed in patients with malignancy, the mean decrease being more significant in the earlier stages than in advanced malignancy, the degree of fall in serum copper level depending on the amount of reduction in tumour mass.

The role of copper in malignancy is not yet understood. Earlier workers (Sood et al 1976) considered that the rise in serum copper level in malignancy could be due to destruction and necrosis of tissues involved, leading to release of copper present in the affected tissue in the circulation. Thus surgical removal of tumour or highly significant reduction in tumour mass as a result of successful therapy may cause lowering of serum copper level as observed in the present study (Cohen et al (1979) suggested enhanced uptake of copper from the gut as a possible mechanism. Samuni et al (1981) hypothesized that elevated serum copper levels may enhance the formation of hydroxyl radicals which in turn cause nucleic acid damage, thus leading to a malignant process.

The identification of interfering substances or conditions is of utmost importance to avoid misinterpretation of copper level. Pregnancy oestrogen therapy and contraceptive drugs are frequent causes of serum copper elevations, serum copper levels is

in infections, liver disease, acute leukaemias and Hodgkin's disease and several other malignancies. These conditions have to be carefully excluded.

The present study shows a possible role of serum copper level in the diagnosis and management of premalignant and malignant gynaecologic lesions. The correlation found in this study between serum copper levels and the extent of premalignant and malignant disease, and the decrease following successful treatment, confirm that serum copper determination is a useful parameter in evaluating the activity and diffusion of neoplasia and therapeutic results in gynaecologic malignancies. The simplicity of this test lends further impetus for its wider application in the management of malignancies. Serum copper level appears to represent a reasonably sensitive, although non-spe-

cific auxilliary test in the management of premalignant and malignant conditions of the female genital tract.

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