SERUM COPPER, CERULOPLASMIN AND NON-CERULOPLASMIN COPPER LEVELS IN HYPERPIGMENTARY DISORDERS

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Summary

In 50 controls and 50 patients with hyperpigmentation serum copper, ceruloplasmin and non-ceruloplasmin copper have been estimated. Significantly higher levels of serum copper and non-ceruloplasmin copper have been detected in hyperpigmentary disorders. In toxic melanoderma and in females with melasma the main rise had been in non-ceruloplasmin copper, importance of which has been high-lighted.

The most important determinant pigment for skin colour is melanin. This pigment is synthesised in the melanocytes by conversion of tyrosine under the effect of copper-containing enzyme tyrosinase. In disorders of pigmentation there may be too much or too little of melanin pigment. Hyperpigmentation may be focal or diffuse. Its cause may be obvious or obscure and at times impossible to determine. Disfigurement and resultant psychological trauma caused by hyperpigmentation especially in the females enhances its importance.

As the production of the enzyme tyrosinase depends upon the amount of copper received by melanocytes[1] the importance of this trace element in the process of pigmentation becomes obvious. There are various reports indicating low levels of copper in case of vitiligo[2,3] and higher levels in cases of hyperpigmentation[4].

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Paucity of reports about copper metabolism in commonly met hyperpigmented disorders such as melasma, toxic melanoderma and post dermatitis pigmentation aroused the interest to study this problem in such disorders.

Material and Methods

One hundred persons attending the skin and S.T.D. department of Shri Guru Tegh Bahadur Hospital, Amritsar were included in the present study. Fifty of them were not suffering from any cutaneous or systemic ailment and acted as controls and the other fifty were suffering from various pigmentary disorders such as melasma (24 patients), post inflammatory pigmentation(13 patients), toxic melanoderma (11 patients) and Riehl's melanosis (2 pateints). 9 of these patients had lentigines and 5 had freckles. In each person serum copper[5] and ceruloplasmin[6] were estimated. Serum ceruloplasmin copper was determined by multiplying ceruloplasmin with a factor 3.4 since ceruloplasmin contains copper to the extent of 0.34%[7,8]. Serum non-ceruloplasmin copper was estimated by subtracting this amount from the total copper as follows :

Non - ceruloplasmin copper = Total copper - (Ceruloplosmin x 3.4) ugm%. In controls the complexion was graded as dark, wheatish and fair ; and in patients, the extent of area affected by hyperpigmentation was recorded.

Results

Control group : Serum copper level ranged between 83.3 to 166.6 micrograms% with an average of 113.9 micrograms%. Serum ceruloplasmin level ranged between 15.7 to 27.4 mg% with an average of 19.7 mg%. Serum non-ceruloplasmin copper ranged between 26.9 to 83.3 micrograms% with an average of 48.3 micrograms and comprised 42.3% of the total copper. Statistical differences in levels of total copper, ceruloplasmin and non-ceruloplasmin copper among sexes, age groups and complexion were not significant.

Patients with pigmentary disorders :

These were equally distributed in both the sexes i.e., 25 were males and 25 females ; their ages ranging between 12–50 years. Less than 100 sq. cm. hyperpigmented area was observed in 16 patients ; 101-500 sq. cm. in 13 patients and lesions scattered all over the body or area involved more than 500 sq. cm. in 21 patients.

Statistically significant higher levels of total copper and non–ceruloplasmin copper were observed in pigmentary disorders with an average of 123.5 microgram% and 56.7 micrograms% respectively. Serum ceruloplasmin levels were on an average 19.6 mg%. Non-ceruloplasmin copper comprised 45.9% of total copper (Table 1).

Alterations in the various levels when compared for individual sexes or according to the extent of areas involved in various pigmentary disorders were not statistically significant. The levels of serum copper were highest in toxic melanoderma. The main rise was due to non-ceruloplasmin copper which comprised 51% of the total copper. In melasma non-ceruloplasmin copper levels were higher in females (58.4 microgram%) and comprised 47.5% of the total copper, whereas the levels in males remained unaltered (42.3% of the total copper). These changes among sexes in cases of melasma were not statistically significant. (Table 2).

TABLE 1

Showing serum copper, ceruloplasmin and non-ceruloplasmin in various hyperpigmentary disorders.

	Serum copper (ug%)		Serum ceruloplasmin (mg%)		Serum non-ceruloplasmin (ug%)	
	Range	Average	Range	Average	Range	Average
Melasma (24 cases)	90.9–151 9	118.6	15.1–25.4	19.1	25.6– 95.1	53.6
Post-inflammatory (13 cases)	90.6–181.0	121 2	16.6–26.2	20.0	34.3–103 5	53.1
Toxic melanoderma (11 cases)	106.0–181.7	139.0	15.8–28.0	20.1	34.3–109.3	70.9
Riehl's melanosis (2 cases)	106.0–121.2	113.6	20.1–22.8	21.5	37.7– 43.7	40.9
Total (50 cases)	90.6–181.4	123.5	15.1–28.0	19.6	25.6–109.3	56.7

TABLE 2

Showing serum copper, ceruloplasmin and non-ceruloplasmin copper in both sexes in patients suffering from melasma

	Sex	No. of cases	Range	Average	't' value	Statistical evaluation.
Serum Copper in micrograms%	F	13	90.9-151.9	122.9	1.37	Not significant
	M	11	90.9-136.7	113.5		
Serum Ceruloplasmin in mg%	F	13	15.1- 25.4	19 0	0.32	,,
	M	11	16.6- 22.8	19.3		
Serum non-ceruloplasmin Copper in micrograms%	F	13	25.6- 95.1	58 4	1.61	,,
	M	11	34.5- 72.8	48.0		

Discussion

The average levels of serum copper in controls had been 113.9 microgram%. Among Indian population the levels of serum copper have been reported to vary between 95-150 microgram% [2,4,8,9] Various authors have reported serum ceruloplasmin levels between 23-40 mg%[8,9,10,11]. The levels in the present control cases were comparatively low (19.3 mg%). This may be attributed to their low nutritional status as levels of ceruloplasmin have been shown to be low in gastrointestinal disorders and malnutrition[6,12]. Though serum non-ceruloplasmin copper has been reported to comprise only 4% of total copper[9,13], in our controls this comprised an average 42.3% of total copper (48.2 micrograms%). Lal et al[8] have also reported average non-ceruloplasmin level of 39.15 micrograms%. Levels of copper, ceruloplasmin and non-ceruloplasmin copper compared between sexes, different age groups and complexion did not show any statistically significant change.

The levels of total serum copper and non-ceruloplasmin copper in disorders associated with hyper-pigmentation have been detected to be significantly higher than normal, the latter one comprising a higher percentage (45.9%) of the total copper. Further, rise in copper level has occurred mainly due to non-ceruloplasmin copper. The significant rise in non-ceruloplasmin copper indicates its possible role in the production of tyrosinase oriented melanin pigment, probably by a direct primary stimulus either at the level of production of enzyme tyrosinase or in the process of pigment formation.

The levels of serum copper were highest in toxic melanoderma, the non-ceruloplasmin copper comprising more than 1/2 of the total copper (51%). In post inflammatory hyperpigmentation non-ceruloplasmin copper comprised an average 43.8%, as compared to normal 42.3%, of the total copper. In females with melasma non-ceruloplasmin copper comprised 47.5% of the total copper, whereas in male cases with melasma the levels remained unaltered when compared to normal. In pregnancy rise in levels of copper have been reported to be in direct proportion to rise in level of ceruloplasmin[6,12], whereas in melasma in females ceruloplasmin copper appears to play no role.

In hyperpigmentary disorders such as toxic melanoderma and melasma in females, it appears that non-ceruloplasmin copper plays a certain role either at the site of production of tyrosinase or at the site of production of melanin, in addition to other factors such as exposure to ultraviolet light or alteration in transport of melanin granules.

Kandhari and Sobhanadhri[4] showed high levels of total copper in hyperpigmented cases of toxic melanoderma, chloasma and Riehl's melanosis, and concluded that hypercupremia may be one of the factors contributing to hyperpigmentation.

The rise of non-ceruloplasmin copper in the present cases with hyperpigmentation is not secondary to pigmentation as the extent of hyperpigmented area was not related to the level of non-ceruloplasmin copper. Factors responsible for such a rise whether inherent, acquired or iatrogenic remain unknown. One can only conclude that persons having non-ceruloplasmin cupremia are prone to hyperpigmentation whenever thrown in with other fray of circumstances.

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TRUE or FALSE ?

The 'Pancreatic dermatosis' is characterised by a skin rash, migrating superficial thrombophlebitis, anemia, cachexia and carcinoma of the head of pancreas.

(Answer Page No. 169)