A PROGNOSTIC ROLE FOR CERULOPLASMIN IN THE DIAGNOSIS OF INDOLENT AND RECURRENT INFLAMMATION

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Ceruloplasmin is increased in infections, inflammatory diseases, and neoplastic diseases and may be scarcely visible to the naked eye because it imparts a faint green color to the serum. This poses an interesting question as to a possible prognostic role for ceruloplasmin in the diagnosis of persistent or recurrent infection. The clinical course of 50 patients with tainted serum was reviewed retrospectively and ceruloplasmin levels correlated with diagnosis and outcome. Group I consisted of 20 healthy controls with normal ceruloplasmin levels: 35.1 ± 2.0 mg/dL (range 25 to 45 mg/dL). Group II was made up of 23 surgical patients; 10 of these patients had elevated levels of ceruloplasmin, nine of whom had significant infections (64.2 ± 3.2 mg/dL), and one patient was on estrogen (73.7 mg/dL). Group III consisted of 27 medical patients; 25 of these patients had elevated levels of ceruloplasmin, 20 of whom had infections (54.1 ± 2.6 mg/dL), and five had malignancies (61.0 ± 3.0 mg/dL). Ceruloplasmin levels were consistently elevated in all patients with infections relative to controls ($P<.001$) with a variable response in other disease states. Therefore, ceruloplasmin may be useful as a serum marker for indolent or recurrent infections. (*J Natl Med Assoc.* 1992;84:781-784.)

Key words • ceruloplasmin • tainted serum • copper

Ceruloplasmin is a single polypeptide containing seven copper atoms per molecule, and it functions as an acute-phase reactant similar to C-reactive protein, haptoglobins, α2-macroglobulins, and components of the complement cascade.[1] Its plasma concentration is increased in a variety of conditions including tissue damage, infection, malignancy, and inflammatory disorders.[2] It has three main functions: donation of copper to enzyme systems dependent on that element, an antioxidant activity that protects cells from damage caused by free oxygen radicals, and maintenance of iron in the oxidized ferric state, which decreases the virulence of many bacteria.[3]

Ceruloplasmin imparts a faint green color to serum that is visible to the naked eye of trained laboratory personnel. The chief laboratory technician at one of our affiliated institutions had a 2-year collection of 50 cases of tainted serum and often made accurate predictions about which patients were likely to have indolent or recurrent infections based on failure of their serum to clear. The purpose of this study was to correlate the ceruloplasmin levels in this group of patients with their primary diagnosis and clinical course to determine if the presence of this compound could be used as a biological marker of unresolved infection and inflammation.

METHODS AND MATERIALS

Fifty patients were identified by the chief laboratory

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TABLE 1. DISEASE PROFILE OF GROUP II SURGICAL PATIENTS: PROCEDURES PERFORMED AND CORRESPONDING CERULOPLASMIN LEVELS*

Diagnosis	n	Procedure	Ceruloplasmin Levels†
Infection with or without sepsis	9		64.2 ± 3.2
Diabetic gangrene		Amputation	
Perforated appendix		Appendectomy	
Intra-abdominal abscess		Drainage	
Empyema of chest		Tube thoracostomy	
Infected decubitus ulcers		Debridement	
Malignancy: laryngeal and cervical cancer	2	Surgery and radiation	27.5 ± 1.3
Trauma	5		37.0 ± 1.8
Abdominal trauma		Exploratory laparotomy	
Long bone fractures		Open fixation of fractures	
Inflammation	3		48.1 ± 2.3
Pseudocyst of pancreas		Cystogastrostomy	
Small bowel obstruction		Exploratory laparotomy	
Mediastinal histoplasmosis		Resection of mediastinal granuloma	
Elective surgery	3		
Aorto-bi-iliac disease		Aorto-bi-femoral graft	38.6 ± 1.9
Prepyloric ulcer		Vagotomy/antrectomy	
Severe COPD‡		Tracheostomy	
Mandibular atrophy	1§	Reconstruction	73.7

*N = 23.
†Mean ± SEM.
‡Chronic obstructive pulmonary disease.
§Patient was on estrogen.

technician as having green tainted serum from 1987 to 1989. The ceruloplasmin level of these sera was measured immunochemically by single radial immunodiffusion using commercially available kits. The normal range was 25 mg/dL to 45 mg/dL. Twenty patients (Group I) without infections, neoplasms, or recent surgery were randomly obtained and used as controls. Their ceruloplasmin levels averaged 35.1 ± 2.0 mg/dL. Among the 50 patients, 23 underwent either elective or emergency operations and were designated as Group II. The remaining 27 patients had a variety of medical illnesses and constituted Group III. Patients in Groups II and III underwent treatment for their various disease processes with follow-up ceruloplasmin levels. All patients had baseline bilirubin, albumin, and white blood cell counts done. The disease profile of Groups II and III is shown in Tables 1 and 2, respectively.

RESULTS

The bilirubin, albumin, and white blood cell counts for all three groups are presented in Table 3. All 50 patients in Groups II and III had tainted serum that was discernible to the naked eye. In Group II, 10 of 23 patients had elevated ceruloplasmin levels including nine with infections secondary to gangrene, perforated appendix, intra-abdominal abscess, empyema, and infected decubitus ulcers (64.2 ± 3.2 mg/dL). This was statistically significant compared to controls ($P<.001$). The remaining patient who underwent mandibular reconstruction was on estrogen. The patients in Group II with malignancies and trauma, and those who had elective surgery had low or normal ceruloplasmin levels.

In Group III, 25 of 27 patients had elevated ceruloplasmin levels. This included 20 patients with a variety of infections (Table 2), and all patients with advanced malignancies 54.1 ± 2.6 and 61.0 ± 3.0 mg/dL, respectively. The ceruloplasmin levels returned to normal in all patients after treatment, and the serum lost its green tint. Of interest, one medical patient with relapsing pancreatitis had several episodes in which elevated ceruloplasmin levels preceded recurrent clinical infection. Again, this was noted by the chief laboratory technician because of the green tinted serum.

TABLE 2. PROFILE OF GROUP III MEDICAL PATIENTS WITH SPECIFIC ILLNESSES AND CERULOPLASMIN ACTIVITY*

Category of Diseases	n	Specific Illnesses	Ceruloplasmin Levels†
Infection with or without sepsis	20	Osteomyelitis Endocarditis Urosepsis Viral illness Rheumatoid arthritis Chronic relapsing pancreatitis Secondary amenorrhea	54.1 ± 2.6
Advanced malignancy	5	Metastatic breast, renal, and lung cancer	61.0 ± 3.0
Secondary amenorrhea	1		56.0
Salicylate overdose	1		36.3

*N = 27.
†Mean ± SEM.

TABLE 3. PREOPERATIVE HEMATOLOGIC AND BIOCHEMICAL PROFILE OF ALL GROUPS

Group	Bilirubin	Albumin	White Blood Cell Count
I	0.5 ± 0.3	3.9 ± 1.2	9.7 ± 1.85
II	0.55 ± 0.06	3.0 ± 1.5	10.4 ± 0.76
III	0.63 ± 0.9	3.5 ± 0.21	12.1 ± 1.6

DISCUSSION

The rationale for implicating a prognostic role for ceruloplasmin in the diagnosis of untreated and recurrent infection and inflammation is a function of its primary actions as a transporter of copper, its antioxidant activity, and its ferroxidase effect. For example, lysyl oxidase is a copper-dependent enzyme system that is critical in wound healing because it forms cross-links between collagen fibers.[1] As an antioxidant, ceruloplasmin clears free oxygen radicals in a manner similar to the cuproprotein, superoxide dismutase. Free radicals are atoms or molecules with one unpaired electron and hence are extremely reactive. They attack unsaturated lipids that are present in abundance in mammalian cell membranes. They initiate a series of reactions that release radicals and peroxidic products such as hydro, endo, and cyclic peroxides. This in turn leads to an autocatalytic process that ultimately destroys the lipid molecule. Ceruloplasmin clears both the free radicals and the peroxidic products.

Ceruloplasmin keeps iron in the oxidized ferric state thus preventing it from undergoing the redox cycle (ferric ⇕ ferrous) necessary for bacteria to initiate their toxic effects. This is referred to as the ferroxidase effect of ceruloplasmin. Bacteria need iron in the ferrous state to be pathogenic. Through this action, ceruloplasmin acts to inhibit bacterial cell growth. The patients in both the medical and surgical groups with infection, sepsis, and inflammation all had elevated ceruloplasmin levels and green-tinted serum. After the appropriate treatment, the levels returned to normal and the serum became normal in color.

In 1980, Hallbook and Hedelin reported that ceruloplasmin levels in postoperative patients initially decreased but began to increase by day three.[4] In 1982, Gregoriadis et al measured serum copper levels in patients undergoing elective herniorrhaphy, cholecystectomy, and colectomy including abdominoperineal resection.[5] The hernia group had normal levels preoperatively that increased significantly after the second postoperative day. Patients in the other two groups had high levels preoperatively that dropped by the second postoperative day and did not begin to rebound until the fourth day. They concluded that patients with malignancies and inflammatory processes preoperatively already had high levels and could not immediately respond to the stress of surgery. This was consistent with our findings in the subsets of our surgical group with neoplasms and inflammatory disorders who had low or only borderline elevations in their ceruloplasmin levels. We were unable to explain why the trauma patients in the surgical group did not have elevated levels postoperatively. All were previously healthy, young adults who were acutely injured. Similarly, our three elective surgical patients all had normal levels postoperatively.

Elevated ceruloplasmin and copper levels are found in females taking estrogen-based oral contraceptives. The only patient in our surgical group without infection who had an elevated ceruloplasmin level was on estrogen when he underwent reconstruction for mandibular atrophy.

SUMMARY

The data suggest that ceruloplasmin correlates well with infections and inflammatory disorders, but has a

variable and unpredictable response in patients with malignancies, trauma, and in patients undergoing elective surgery. Therefore, it may be of prognostic use in following patients with indolent infections or recurrent inflammatory disorders.

Literature Cited

1. Gutteridge JMC, Stocks J. Ceruloplasmin: physiological and pathological prospectives. *Crit Rev Clin Lab Sci.* 1981;14:257-313.

2. Michelson AM, McCord JM. *Superoxide and Superoxide Dismutases.* New York, NY: Academic Press; 1977.

3. Poulik MD, Weiss ML. *Ceruloplasmin in the Plasma Protein.* Vol 2, 2nd ed. New York, NY: Academic Press; 1975.

4. Hallbook T, Hedelin H. Changes in serum copper and serum ceruloplasmin concentration induced by surgical trauma. *Acta Chir Scand.* 1980;146(suppl 6):371-373.

5. Gregoriadis GC, Apostolidis NS, Romanos AN, Paradellis TP. Postoperative changes in serum copper value. *Surg Gynecol Obstet.* 1982;154:217-221.