10.5005/jp-journals-10051-0086

REVIEW ARTICLE

Copper Deficiency leading to Hematological and Neurological Dysfunction caused by Consumption of Zinc-containing Denture Adhesives

[1]Priyanka Konin, [2]Chandrashekar Sajjan, [3]Nagesh M Ingleshwar

ABSTRACT

The purpose of this article is to review the literature that documents the systemic adverse effect of excessive use of zinc-containing denture adhesive. Chronic, excess zinc intake can result in copper deficiency, and low copper serum level causes hematological and neurologic dysfunction. The root cause of excessive zinc ingestion from denture adhesives in patients is poorly fitting dentures. Dentists often advise their denture patients that their prostheses will require periodic relining or remaking as residual ridge resorption occurs over time. This message needs to be better communicated to the public, along with the dangers of overuse of denture adhesives.

Keywords: Denture adhesive, Hyperzincemia, Hypocupremia, Zinc-free denture adhesives.

How to cite this article: Konin P, Sajjan C, Ingleshwar NM. Copper Deficiency leading to Hematological and Neurological Dysfunction caused by Consumption of Zinc-containing Denture Adhesives. Int J Oral Care Res 2017;5(1):71-74.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Denture cream, which is used by millions of denture wearers, has recently been linked to hyperzincemia and thus hypocupremia. Although zinc is an essential part of a healthy diet, excessive zinc intake can lead to serious side effects. The use of denture adhesives/fixatives began about the same time as the age of modern dentistry in the late 18th century. The use of denture adhesive to aid in the retention and function of denture provides the psychological benefit for the patient, thus improving the quality of life of edentulous patients. Many case reports are documented in the literature regarding the adverse effect of excess use of zinc-containing denture adhesive. Zinc salts were introduced into copolymer mixtures of lower alkylvinyl ether – maleic acid blends that were invented by Shah et al in 1988 to stabilize denture adhesives. Excess ingestion of zinc into the small intestine results in copper deficiency. Copper is a trace element that acts as an essential cofactor in many enzymatic reactions vital to the normal function of the hematological, vascular, skeletal, and neurological systems.[1]

Excessive zinc intake causes upregulation of metallothionein zinc-binding protein in enterocytes, which has a high affinity for copper. Thus, when the enterocytes are sloughed into the gastrointestinal tract, significant amounts of copper are lost and can eventually cause a copper-deficient state.[2]

Copper deficiency is known to cause all forms of anemia (macrocytic, microcytic, or normocytic), leukopenia, neutropenia, and rarely thrombocytopenia.[3-6] Although not pathognomonic, copper deficiency is associated with bone marrow findings of vacuolated myeloid and erythroid precursors, ringed sideroblasts, and multilineage dysplasia.

More recently, copper deficiency has been shown to cause neurological complications, particularly a myelopathy, i.e., clinically and radiologically similar to that caused by vitamin B12 deficiency.[7-9] Other neurological associations have also been described, including neuropathy, motor neuron disease, and demyelination. The purpose of this article is the review of the literature that documents the systemic adverse effect of excessive use of zinc-containing denture adhesive.

REVIEW

The US Food and Drug Administration received reports of adverse systemic effects from the overuse of denture adhesives at least as early as 2005. Willis et al[10] reported three cases of zinc-induced copper deficiency in which the diagnosis first was suggested based on the bone marrow examination. The first patient was a 47-year-old man with a debilitating peripheral neuropathy that had progressed during the previous 18 months, mild anemia, and severe neutropenia. The cause of the zinc excess remained undetermined. The second was a 21-year-old

[1,3]Senior Lecturer, [2]Reader

[1,2]Department of Prosthodontics, AME'S Dental College and Hospital, Raichur, Karnataka, India

[3]Department of Prosthodontics, S. Nijalingappa Institute of Dental College Sciences & Research, Kalaburagi, Karnataka India

Corresponding Author: Priyanka Konin, c/o Avinash Gadwal H:No 1-11-133, Nijalingappa Colony, Raichur, Karnataka, India Phone: +919844993727, e-mail: priyankakonin@gmail.com

man receiving zinc supplementation for acrodermatitis enteropathica in whom moderate normocytic anemia and neutropenia developed. The third patient was a 42-year-old man with anemia, severe neutropenia, and a peripheral neuropathy that had progressed during 8 months. This patient revealed consuming an entire tube (68 g) of Poligrip denture cream (containing polymethylvinylether maleic acid calcium-zinc salt) daily for the past 4 to 5 years. The bone marrow findings in all cases suggested copper deficiency, which was confirmed by further laboratory testing and determined to be due to zinc excess. On copper supplementation, all three patients showed a remarkable improvement in hematologic findings; however, the neuropathy showed no improvement.

In 2008, researchers at the University of Texas Southwestern Medical Center published research linking denture cream to zinc poisoning in The Medical Journal Neurology, 2008.[11] Four patients are reported in this study with a history of use of zinc-containing denture adhesive due to ill-fitting dentures. All these patients showed neurological manifestations and changes in the hematocrit values. Serum zinc levels improved in three patients following cessation of denture cream use. Copper supplementation resulted in normalization of copper levels in all four patients, but mild neurologic improvement was noted only in two patients when they stopped using denture cream.

Hedera et al[12] reported 11 patients with hyperzincemia and copper deficiency. Clinical features were quite uniform. Every patient reported numbness and paresthesia affecting the lower extremities and loss of balance. Hematological examination showed anemia and pancytopenia. Neurologic examination showed deficits involving motor sensory polyneuropathy and myelopathy. Bone marrow suppression was evident in all the subjects. Every individual described their dentures poorly fitting and reported applying large amounts of denture cream (Poligrip/Fixodent) on an average daily zinc exposure of 600 to 1200 mg/24 hours. Copper supplementation showed improvement in hematological manifestation with varying degrees of neurological outcome. Few patients showed mild improvement in neurological symptoms and few remained unchanged.

Doherty et al[13] reported a case of 58-year-old male patient who was using three 40 g tubes of zinc-containing denture adhesives per week, a selection of which was found to contain 17 to 34 mg of zinc per tube. He came with a history of difficulty in walking and balance. Blood investigations showed macrocytic anemia, leukopenia, severe neutropenia, low folate, and high ferritin level. Neurological examination was normal initially but progressed by the end of 8th month. He had a spastic paraplegia with loss of all sensory modalities up to the T10 dermatome. In other words, he had features of spinal cord damage (myelopathy). His serum copper level was markedly reduced at 2.0 µmol/L (normal: 10–22 µmol/L) and he was therefore, diagnosed with copper deficiency myelopathy. His symptoms, particularly sensory symptoms, had improved slightly on copper supplements, but he was still wheelchair-bound and catheterized and had very little power in his legs.

Barton et al[14] reported a 50-year-old man who presented with a 4-year history of unsteadiness, with recent falls and tingling in his fingers. Neurological examination found an ataxic gait, with a positive Romberg's sign. There was distal wasting and weakness in all four limbs and impaired coordination, with pseudoathetosis in the arms. Biochemical investigations, however, showed an undetectable ceruloplasmin (0.085 g/L), a very low serum copper (1.1 mmol/L), and a markedly raised serum zinc (38.2 mmol/L). He gives the history of ill-fitting dentures, requiring excessive use of the denture fixative Poligrip Ultra (GlaxoSmithKline, Brentford, UK), known to have high zinc content (38 mg of zinc per gram). He had been using approximately two to three tubes per week, for 3 to 4 years. On copper supplementation for 3 months, the clinical neurological features were unchanged, but there was no further neurological deterioration. Anemia, leukopenia, and neutropenia had resolved and the ceruloplasmin, copper, and zinc concentrations are now falling within the respective healthy population.

Gabreyes et al[15] reported a study done by Scottish Trace Element and Micronutrient Reference Laboratory at Glasgow. Sixteen patients with low copper measurements (<6 µm) were selected from the existing clinical database. The clinician in charge of the patient was approached for clinical history and examination. Full blood count, bone marrow morphology, cytogenetics, serum zinc concentration, and imaging (where available) were reviewed and compared following the correction of low copper concentration. It was determined that 86% had both hematological and neurological features of copper deficiency, while 18% had hematological features only at presentation. Twelve of the sixteen patients had high serum zinc concentrations (>18 µm/L), nine patients were using zinc-containing dental fixatives at the time of diagnosis. 94% of patients had hematological features as an initial manifestation of copper deficiency, which included anemia, thrombocytopenia, and neutropenia. Patients who underwent later bone marrow testing had appearances in keeping with refractory cytopenia with multilineage dysplasia, refractory anemia with excess of blasts, unclassified marrow dysplasia, or probable myelodysplasia; 75% of patients had neurological symptoms or signs, including progressive walking difficulties and paresthesia, or gait difficulties without sensory signs.

Magnetic resonance imaging (MRI) showed multifocal T2 hyperintense foci in the subcortical white matter, and atrophy of the cerebrum and cerebellum was also seen on computerized tomography. The MRI of the spinal cord showed signal change in the dorsal columns in either the cervical or thoracic cord; 93% of cytopenias responded to copper replacement and addressing the original cause of the copper deficiency, but only 25% of patients had improvement in their neurological function, while 33% deteriorated and 42% remained unchanged.

Crown and May[16] reported a 36-year-old female with bone marrow failure, myelodysplastic syndrome, peripheral neuropathy, and a gait disturbance. She gave a history of use of denture adhesive. Labs were then obtained demonstrating she had dramatic and unsuspected hypocupremia and hyperzincemia. Administration of copper and cessation of denture adhesives resulted in recovery of her hematopoietic system and partial resolution of the neurological sequela.

Prasad et al[17] reported a 65-year-old woman with Crohn's disease, presented with perioral paresthesia and a burning sensation in the mouth. Initial blood tests including serum ferritin, vitamin B12, and folate were normal apart from mild pancytopenia. Serum copper was low, in spite of receiving regular copper in her parenteral feeds. The copper in her parenteral feeds was increased initially, but when it did not improve, she was started on weekly IV copper infusions. She was using dental adhesive, which had zinc in it, and a possibility that this was causing her copper deficiency to be raised. Serum zinc levels were normal, but urinary zinc was very high. The patient was advised to use zinc-free dental adhesive and her copper level returned to normal within a few months with normalization of her pancytopenia, and partial resolution of her oral paresthesia.

DISCUSSION

Copper deficiency is a well-established and increasingly recognized cause of neurologic and hematologic disease.[8,9] Acquired copper deficiency can result from gastrointestinal surgery, malabsorption, and parenteral feeding deficiency.[9] In addition, excess zinc ingestion in the form of denture adhesive has also been established as a cause of hypocupremia.[9]

This literature review documents the serious adverse effects of use of denture adhesives leading to hyperzincemia and hypocupremia. Copper is a trace element that acts as an essential cofactor in many enzymatic reactions vital to the normal function of the hematological, vascular, skeletal, and neurological systems.[18] Ingestion of excess zinc in the form of zinc supplements and denture cream has been associated with copper deficiency.

The recommended dietary allowance for zinc is 11 mg/day for men and 8 mg/day for women. Lower zinc intake is recommended for infants (2–3 mg/day) and children (5–9 mg/day) because of their lower average body weights.[18] The estimated daily zinc exposure by use of denture adhesive was between 350 and 1,700 mg/day.[12] Zinc concentration in denture creams (Fixodent original, Poli-Grip original, Poli-Grip Polyseal) was analyzed by dynamic reaction cell inductively coupled plasma mass spectrometry and was found to be: Fixodent original – 17,283 µg/g zinc, Poli-Grip original – 34,190 µg/g zinc, and Poli-Grip Polyseal – 27,531 µg/g zinc.[11] Therefore, these patients using denture adhesives were more likely to consume excess zinc orally.

The root cause of excessive zinc ingestion from denture adhesives in patients is poorly fitting dentures. Although dentures are fabricated to meet the demands of edentulous patients, the retention, stability, and functionality of complete dentures are affected by residual ridge resorption (RRR). Multiple methods can be utilized to overcome RRR, including dental implant therapy, overdenture attachments anchored to natural teeth, denture relines, and rebases and denture adhesive.[19]

Dentists often advise their denture patients that their prostheses will require periodic relining or remaking as RRR occurs over time. Too often, patients resort to the use of denture adhesives to compensate for the space that develops over time between denture bases and the underlying mucosa. As more alveolar supporting bone is lost, such patients may use more adhesive. Instead, they need to have loose-fitting dentures relined or remade to regain the retention they seek. This message needs to be better communicated to the public, along with the dangers of overuse of denture adhesives, as well as the availability of zinc-free denture adhesive. Zinc-free denture adhesives available are Super Poligrip Free, Super Poligrip Comfort Seal Strips, Super Poligrip Powder, Protefix, Fittydent Super Adhesive Cream, Secure Denture Bonding Cream, Secure Denture Adhesive Cushion Strips, Seabond Denture Adhesive seals, Effergrip.

CONCLUSION

Prolonged heavy usage of zinc-containing denture adhesives causes the absorption of zinc compound into the body, causing an overdose effect. Elevated level of zinc will lead to depletion of copper in the bloodstream, resulting in neurologic disorder, such as paresthesia, anemia, pancytopenia, bone marrow failure. Denture wearers need to be educated about the ill-effects of use of zinc-containing denture adhesives and must be emphasized on nonzinc-containing denture adhesives.

REFERENCES

1. Shah NB, Gounaris MC, Holeva KT. Inventors: Richardson-Vicks, Inc, assignee. Denture stabilizing zinc and strontium salts of AVE/MA copolymer. US patent 4 758 630. July 19, 1988.
2. Fiske DN, McCoy HE, Kitchens CS. Zinc-induced sideroblastic anemia: report of a case, review of the literature, and description of the hematologic syndrome. Am J Hematol 1994 Jun;46(2):147-150.
3. Halfdanarson TR, Kumar N, Li CY, Phyliky RL, Hogan WJ. Hematological manifestations of copper deficiency: a retrospective review. Eur J Haematol 2008 Jun;80(6):523-531.
4. Kumar N, Low PA. Myeloneuropathy and anemia due to copper malabsorption. J Neurol 2004 Jul;251(6):747-749.
5. Dunlap WM, James GW III, Hume DM. Anemia and neutropenia caused by copper deficiency. Ann Intern Med 1974 Apr;80(4):470-476.
6. Wasa M, Satani M, Tanano H, Nezu R, Takagi Y, Okada A. Copper deficiency with pancytopenia during total parenteral nutrition. JPEN J Parenter Enteral Nutr 1994 Mar-Apr;18(2): 190-192.
7. Schleper B, Stuerenburg HJ. Copper deficiency-associated myelopathy in a 46-year-old woman. J Neurol 2001 Aug;248(8): 705-706.
8. Kumar N, Gross JB Jr, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology 2004 Jul;63(1):33-39.
9. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc 2006 Oct;81(10):1371-1384.
10. Willis MS, Monaghan SA, Miller ML, McKenna RW, Perkins WD, Levinson BS, Bhushan V, Kroft SH. Zinc-induced copper deficiency: a report of three cases initially recognized on bone marrow examination. Am J Clin Pathol 2005 Jan;123(1):125-131.
11. Nations SP, Boyer PJ, Love LA, Burritt MF, Butz JA, Wolfe GI, Hynan LS, Reisch J, Trivedi JR. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology 2008 Aug;71(9):639-634.
12. Hedera P, Peltier A, Fink JK, Wilcock S, London Z, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin. II. The denture cream is a primary source of excessive zinc. Neurotoxicology 2009 Nov;30(6):996-999.
13. Doherty K, Connor M, Cruickshank R. Zinc-containing denture adhesive: a potential source of excess zinc resulting in copper deficiency myelopathy. Br Dent J 2011 Jun;210(11): 523-525.
14. Barton AL, Fisher RA, Smit GDP. Zinc poisoning from excessive denture fixative use masquerading as myelopolyneuropathy and hypocupraemia. Ann Clin Biochem 2011 Jul;48 (Pt 4):383-385.
15. Gabreyes AA, Abbasi HN, Forbes KP, McQuaker G, Duncan A, Morrison I. Hypocupremia associated cytopenia and myelopathy: a national retrospective review. Eur J Haematol 2012 Nov;90(1):1-9.
16. Crown LA, May JA. Zinc toxicity: denture adhesives, bone marrow failure and polyneuropathy. Tenn Med 2012 Feb;105(2):39-40, 42.
17. Prasad R, Hawthorne B, Durai D, McDowell I. Zinc in denture adhesive: a rare cause of copper deficiency in a patient on home parenteral nutrition. BMJ Case Rep 2015 Oct;2015:ii.
18. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc 2001 Mar;101(3):294-301.
19. Duqum I, Powers KA, Cooper L, Felton D. Denture adhesive use in complete dentures. Clinical recommendations and review of the literature. Gen Dent 2012 Nov-Dec;60(6):467-477.