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ORIGINAL ARTICLE

Iatrogenic copper deficiency: Risks and cautions with zinc prescribing

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Aims: Copper deficiency resulting from prescribing zinc in high doses is a rare but life-changing diagnosis that is frequently overlooked. The aim of this study is to gauge how often zinc-induced copper deficiency is missed, to raise awareness of the condition and to stress the need for guidelines for prescribing zinc.

Methods: Suspected cases of zinc-induced copper deficiency were retrospectively obtained by selecting those patients with hyperzincaemia and hypocupraemia from the database of the Scottish Trace Element Laboratory. Case records were reviewed to determine the validity of the suspected diagnosis.

Results: After exclusions, 23 instances of high serum zinc and low serum copper concentrations were found. A positive diagnosis of zinc-induced copper deficiency was made in 14 patients, of which 7 (50%) were previously undiagnosed.

Conclusion: Serum zinc and copper concentrations are rarely measured in patients prescribed zinc and so the vast majority of cases of zinc-induced copper deficiency are likely to be undiagnosed. We recommend the current official advice on the dose and frequency of zinc administration is revised in order to limit, and potentially eradicate, the condition.

KEYWORDS
copper, deficiency, zinc

1 | INTRODUCTION

Zinc-induced copper deficiency (ZICD) is a specific form of copper deficiency associated with ingestion of excessive quantities of zinc. Its diagnosis is often overlooked and can result in anaemia and severe irreversible neurological complications.[1]

Absorption of zinc is largely controlled in the epithelial cells of the small intestine. An increase in zinc intake stimulates a corresponding increase in production of an epithelial protein, metallothionein, which binds zinc and blocks its release from the epithelium into the body.[2,3] However, copper binds more avidly to this protein and, if zinc intake is sufficiently high, this can result in a more complete block to the absorption of copper and ultimately copper deficiency.[4,5]

In its early stage, ZICD presents with anaemia and neutropenia, which resolve if the source of zinc is removed. More often, however, the condition is not diagnosed until the development of neurological sequelae which are often resistant to treatment leading to long-term disability.[6] In the 2 largest series of patients with ZICD, the median times from presentation to diagnosis were 1.1 and 1.0 years by which time 34 of 40 patients (85%) and 9 of 16 (56%), respectively, had developed neurological disease.[1,7]

There is also evidence that some patients with ZICD are not diagnosed at all; for example, in an audit of patients prescribed zinc, unexplained haematological and neurological symptoms typical of copper deficiency were found in 6 of 70 cases (9%).[8]

In the vast majority of patients with ZICD, serum concentrations of zinc and copper are, respectively, high and low.[9] Findings of

hyperzincaemia or hypocupraemia on their own are rare, making a combination of the 2 suggestive of a diagnosis of ZICD. This therefore offers an alternative means of diagnosis. Following an upgrade of the analytical equipment in the NHS Scotland Trace Element Laboratory, simultaneous measurement of >1 analyte became possible for the first time. For logistical reasons, it was decided to measure both serum copper and zinc and only report the analyte requested. This facilitated the copper concentration to be checked in hyperzincaemic samples and similarly, a check of the serum zinc concentration in samples with a low serum copper concentration. On the first 3 occasions that a combination of high zinc/low copper concentrations was found, the possibility of ZICD was suggested to the requesting clinician and in 2 cases the diagnosis was subsequently confirmed. This finding prompted the retrospective survey that is reported here.

What is already known about this subject

- Zinc-induced copper deficiency, a life-changing and occasionally fatal condition, arises as a result of excess ingestion of zinc.
- The diagnosis is frequently delayed due to lack of awareness of the condition leading to irreversible neurological consequences.
- The most common cause is iatrogenic resulting from excess zinc prescribing.

What this study adds

- The vast majority of patients with iatrogenic zinc-induced copper deficiency remain undiagnosed.
- We recommend that current zinc prescribing guidelines are modified in order to prevent copper deficiency.

2 | METHODS

All simultaneous serum copper and zinc results measured over a 13-year period (2005 to 2017) were downloaded from the database of the NHS Scotland Trace Element Laboratory. Zinc and copper were measured by inductively coupled plasma mass spectrometry; analytical performance in the UK national external quality assurance scheme was good throughout the 13 years of the study. The case records of patients with high zinc and low copper results were requested. Serum zinc concentrations above 18 µmol/L, the upper limit of the reference range, were considered to be high, and a serum copper concentration below 8 µmol/L, being the highest value found in literature reports of ZICD,[10] (see Supporting Information) was used to represent a low concentration. The following data were extracted wherever available: presenting symptoms or diagnosis, evidence of excess zinc ingestion, time period of any zinc ingestion and the presence of haematological and neurological symptoms typical of ZICD.

This study was approved by the NHS Greater Glasgow and Clyde research ethics committee and followed Caldicott guidelines.

3 | RESULTS

Over the period of study, the Scottish Trace Element Laboratory database held 16 197 results in 9090 patients in whom serum copper and zinc were simultaneously measured. The combination of high zinc and low copper concentrations was found in 40 (0.44%) patients. Seventeen patients were excluded: 3 had died and the case records destroyed; 2 were receiving total parenteral nutrition; 7 were receiving zinc treatment for Wilson's Disease; the case records for 5 were not available. Results for the remaining 23 patients are shown in Table 1.

Seven patients (30%; Cases 1–7), all of whom had haematological and neurological symptoms, had been referred to neurologists who diagnosed ZICD. In each case, the cause was over-application of zinc-containing dental fixative.

In 7 patients (30%; Cases 8–14), a retrospective diagnosis of ZICD was made. (Cases 8 and 9 were 2 of the patients discussed in the introduction and have been reported in full elsewhere.[9,11]) All had typical symptoms of ZICD, which resolved when the source of ingested zinc was removed. Five patients had been prescribed 3 tablets of Solvazinc/day (135 mg/day). Two patients had over-applied dental fixative. A further 2 patients (Cases 15 and 16) who had been prescribed 135 mg/day zinc had no symptoms of ZICD. (Note: elemental doses of zinc are quoted here and throughout.)

Case 17 was in intensive care and undergoing management of *Legionella pneumophila* infection. She was receiving 39 mg zinc/day via an enteral feed and had haematological and neurological symptoms typical of ZICD.

The 6 remaining patients (Cases 18–23) had no record of high oral intake of zinc in their case records. Three of these patients had typical symptoms of ZICD that could not be explained by their coexisting diagnoses.

The duration of zinc prescribing was only recorded for 2 patients; 7 months in Case 12 and 72 months in Case 14.

4 | DISCUSSION

Previous studies have already demonstrated significant delays in making a diagnosis of ZICD.[1,7] The current study has shown that of the 14 confirmed cases of ZICD, only 7 were diagnosed by the treating clinician. The remaining 7 (50%) were undiagnosed until the change in practice in the Scottish Trace Element Laboratory described earlier, or as a result of this retrospective audit. Five of these patients had been prescribed 135 mg zinc/day. A further 2 patients were prescribed 135 mg zinc/day and were asymptomatic.

TABLE 1 Details of patients.

Case number	Sex	Age (years)	Serum copper (μmol/L)	Serum zinc (μmol/L)	Presentation/diagnosis	Haematology	Neurology	Zinc dose (mg/day)	Outcome
1	F	37	0.6	26.0	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
2	F	38	0.5	31.6	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
3	M	64	0.8	27.2	Dental fixative ZICD	Neutropenia	Myelodysplasia	Unknown	Only haematology resolved
4	F	63	4.9	28.0	Dental fixative ZICD	Anaemia	Myelodysplasia	Unknown	Only haematology resolved
5	M	68	2	33.0	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
6	F	54	0.6	29.8	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
7	F	59	0.8	33.3	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
8	F	54	1.9	27.9	Dental fixative ZICD	Neutropenia	-	Unknown	Only haematology resolved
9	F	51	1	21.0	Pain	Anaemia, neutropenia	Myelodysplasia	135	Only haematology resolved
10	F	21	7	19.5	Anorexia nervosa	Anaemia, neutropenia	-	135	Resolved
11	F	81	6.6	20.5	Severe leg ulcer	Anaemia	-	135	Resolved
12	M	45	2	18.5	Burns	Anaemia,	Peripheral neuropathy	135	Unknown
13	F	7	6	24.6	Fever	Neutropenia	-	135	Resolved
14	M	76	1.3	32.9	Dental fixative ZICD	Anaemia, neutropenia	Myelodysplasia	Unknown	Only haematology resolved
15	M	65	2	30.5	Giardiasis	-	-	135	-
16	F	69	4.2	22.5	Aphthous ulcer	-	-	135	-
17	F	72	2.9	22.3	Legionella, sepsis	Anaemia	Peripheral neuropathy	39	Resolved
18	F	48	5	34.5	Burns	Anaemia	-	-	Unknown
19	M	32	6.4	18.6	Biliary colic	-	-	-	-
20	M	40	5.5	20.0	Systemic sclerosis	-	-	-	-
21	M	71	3.4	23.6	Diabetes	Anaemia	-	-	Unknown
22	F	44	4.4	25.1	Epilepsy	Anaemia, neutropenia	Gait disorder	-	Unknown
23	M	62	5	20.0	Wegener's granulomatosis. Renal failure.	-	-	-	-

It is unclear if Patient 17, who was receiving 39 mg zinc/day through an enteral feed, had ZICD. Although she had symptoms typical of ZICD, these may have been secondary to her severe ill-health; she was in intensive care at the time and although copper is a positive acute phase reactant, very low copper concentrations are not uncommon in very ill patients. However, her urinary zinc concentration was measured and was found to be modestly elevated at 24.3 μmol/L (reference range: 3–19 μmol/L) suggesting that she may have been receiving zinc in excess to requirements.

In 6 patients with low serum copper and high serum zinc concentrations, there was no record in case notes of zinc being prescribed. Three of these patients had symptoms in keeping with ZICD and which were atypical of their underlying diagnosis. However, we do not discount the possibility of ZICD in these patients given a previous report that described the frequent omission in case records of zinc prescribing, other than its initial entry on the prescription sheet.[8] A possible reason for this is that some clinicians may consider zinc to be an essential, innocuous nutrient rather than a pharmaceutical agent with a serious potential side-effect profile.

There was little information recorded in case records on the time period over which zinc was prescribed. In literature reports, ZICD apparently develops slowly over many months or years. However, the condition can occur within a few months,[12,13] suggesting that this apparent slow onset results from a delay in diagnosis.

The risk in the UK of ZICD secondary to over-application of dental fixative or ingestion of over-the-counter zinc tablets is now likely to be very small. In recent years, dental fixatives have been reformulated as zinc-free products. Likewise, all 12 cases of excess ingestion of zinc through over-the-counter formulations reported in the literature occurred in the USA. The maximum zinc preparation available in the UK is Solvazinc which contains 45 mg/tablet; although higher than the Recommended Daily Allowance (5.5 to 9.5 mg/day in men and 4–7 mg/day in women[14]), this is unlikely to be dangerous unless >1 tablet is consumed each day. Nevertheless, this possibility must still be considered; since the current survey, the Scottish Trace Element Laboratory detected ZICD in a middle-aged American woman with unexplained anaemia who had been taking zinc supplements purchased over the counter (amount unknown).

The cases of ZICD identified in the present study were associated with doses of 135 mg zinc/day, which is >10 times higher than the Recommended Daily Allowance. This dose is not evidence-based since no clinical studies have been carried out to establish the optimal dose for treating the milder cases of zinc deficiency occasionally seen in the UK. Nevertheless, it is in line with the British National Formulary recommended adult dose of 45–135 mg zinc/day.[15] A review of case records of patients prescribed zinc found that the higher dose of 135 mg/day was most commonly prescribed (in 52% of the cohort of 70 patients with an additional 8% being prescribed higher doses).[8] By comparison, the first cases of severe zinc deficiency described in Iran in the 1970s were successfully treated with 21 mg/day.[16]

Authoritative international bodies suggest that a single Solvazinc tablet containing 45 mg of zinc may be excessive; the upper tolerable limit for oral zinc intake has been variously calculated at 25 mg/day (UK Food Standards Agency, European Commission),[17,18] 45 mg/day (World Health Organization)[19] and 60 mg/day (US Environmental Protection Agency).[20]

A strong physiological case against the ingestion of large amounts of zinc can also be made. The metallothionein-mediated mechanism that controls zinc homeostasis results in the majority of ingested zinc being either malabsorbed, hyperexcreted or accumulated in bone. As the oral intake of zinc is increased, its absorption from the intestine is reduced to as low as 20% with the majority of ingested zinc being excreted in the faeces.[21] Of the 20 literature reports in which urinary zinc was measured in ZICD patients (see Supporting Information), very high concentrations were recorded: average, 5.0 times the upper normal limit; range, 1.6–17.3 times the upper normal limit. The accumulated zinc stores in bone may even result in elevated urine concentrations for several years.[22]

Hypozincaemia, especially in hospitalized patients, is usually due to the systemic inflammatory response (SIR) rather than zinc deficiency. Around 60% of circulating zinc is bound to albumin much of which is redistributed into the extravascular space during an SIR, thus resulting in low serum zinc concentrations.[23] For example, in healthy patients admitted for elective knee surgery, serum zinc concentrations fall by up to 40% but return to normal values after around a week.[24] It is likely that zinc is often inappropriately prescribed in patients with hypozincaemia secondary to the hypoalbuminaemia associated with an SIR.[9]

In summary, this study has revealed that ZICD is likely to be considerably more common than currently realized. In this study, 50% of patients with ZICD had previously been undiagnosed. Moreover, this figure is likely to be a significant underestimate because these cases were only detected fortuitously following serum zinc measurement, an assay that is infrequently requested in patients prescribed zinc.[8] Failure to make a diagnosis of ZICD increases the subsequent risk of potentially irreversible life-changing neurological sequelae.

5 | CONCLUSIONS

In this survey, we have shown that iatrogenic ZICD is significantly under-diagnosed, resulting in potentially serious irreversible neurological sequelae. The condition is avoidable since it is invariably caused by prescribing zinc in unnecessarily high doses of over 100 mg/day of zinc. The risks of prescribing high doses of zinc was appreciated by Porter in 1977: 'The current dose of 220 mg of zinc sulphate 3 times a day (equivalent to 135 mg/day) may be too high for long-term therapy and a lower dose formulation of 10 or 20 mg capsules may need to be considered'.[25] This was restated more recently by Maret and Sandstead: 'For practical purposes and until research indicates otherwise, zinc intakes should probably not exceed 20 mg zinc in adults'.[26]

We believe our study presents powerful evidence of the risk of iatrogenic copper deficiency associated with exogenous zinc supplementation. The current prescribing advice in the British National Formulary for adults (body weight 31 kg and above) is 45 mg, 1–3 times a day. We suggest that this advice, for both dose and frequency of administration, is revised downwards and that formal guidelines on

the management of conditions requiring zinc supplementation are introduced to minimize the risk of ZICD.

In the absence of current evidence to support a specific safe and efficacious dose, we suggest that when treating nutritional zinc deficiency, prescribed doses should not exceed 20 mg/day of zinc (roughly equivalent to half a Solvazinc tablet/day). The amount of zinc required for the treatment of dermatological conditions such as acrodermatitis enteropathica[27] and acne[28] is currently based on literature studies that invariably employ doses of >100 mg/day. Unless future studies show that lower doses are efficacious we recommend regular monitoring of serum copper concentrations in this indication.

AUTHOR CONTRIBUTIONS

Andrew Duncan wrote the article, and Ian Morrison and Scott Bryson reviewed and suggested improvements to the article.

CONFLICT OF INTEREST STATEMENT

None to disclose.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

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