Inappropriate trace element testing in the Auckland region

David Song, Barry Palmer, Stephen du Toit, James S Davidson

Abstract

Aim To understand recent changes in trace element test usage in the Auckland region of New Zealand.

Methods Laboratory records of trace element tests between 2004 and 2008 were analysed. A questionnaire was sent to a frequent requestor group to elicit reasons for requesting trace element tests.

Results The annual number of trace element test requests increased by 3.5-fold over the study period. The increase was largely due to a 2.8-fold increase in serum copper, a 3.8-fold increase in serum zinc, and a 3.4-fold increase in serum selenium tests. Most of the increase was accounted for by a small number of requestors, mainly general practitioners. An outlier group of 24 requestors was identified who were responsible for ordering 55% of serum copper, 61% of serum zinc, 63% of serum selenium and 66% of blood mercury tests in the last year of the study. Responses to the questionnaire suggest that among the outlier group the reasons for requesting serum zinc, copper and selenium tests are not evidence-based.

Conclusion The majority of trace element tests performed in the Auckland region appear to be non-evidence-based, and represent a significant wastage of public laboratory resources. This suggests that laboratories could achieve significant savings in expenditure by clearly defining appropriate indications for performing trace element tests.

The trace elements zinc, copper and selenium are necessary for many biochemical functions. Deficiencies of these elements occur in the settings of malnutrition and malabsorption, and measurement of serum levels are useful in the management of patients with gastrointestinal disorders and especially in parenteral nutrition. Measurement of serum and urine copper levels are also useful in the diagnosis and management of Wilson's disease and in rare genetic disorders of copper metabolism. These tests are also of value in occasional cases of zinc, copper and selenium poisoning.

Measurement of whole blood and urine mercury are of value in monitoring workplace exposure and in mercury poisoning.

Unless there is a high pre-test probability of deficiency (i.e. a predisposing condition such as gastrointestinal disease), or toxicity (e.g. workplace exposure or suspicion of Wilson's disease) it has not generally been considered useful to measure serum copper, zinc, selenium or blood mercury in patients in general practice.

Despite this, we report a substantial increase in trace element testing by general practitioners in the Auckland region from 2004 to 2008, and describe the results of a questionnaire aimed at understanding the reasons for this increase.
Methods

Labplus is the tertiary referral laboratory for trace element testing for Auckland City Hospital and other hospitals in the Auckland region of New Zealand, and serves a population of approximately 1.5 million. Serum zinc, serum and urine copper, serum selenium, whole blood mercury and urine mercury results from 1 September 2004 to 31 August 2008 were retrieved from the laboratory information system and analyzed to identify trends in trace element testing. These were plasma and serum samples submitted in the course of routine patient care, and had been collected at varying times of day. Serum and plasma samples were treated interchangeably and are referred to collectively as "serum" in this paper.

Serum zinc and copper were measured by flame atomic absorption spectroscopy using a GBC Avanta instrument with an air-acetylene flame. Serum selenium and urine copper were measured by graphite furnace atomic absorption spectroscopy using a Perkin Elmer 4110ZL instrument, which was also used to measure urine mercury and whole blood mercury by flow injection cold vapour atomic absorption spectroscopy. The laboratory participates in the external quality assurance program for trace elements run by Quality Control Technologies Pty Ltd and was accredited by International Accreditation New Zealand to standard ISO15189 during the period of the study.

A questionnaire was sent to the top 24 requestors of trace elements tests, excluding gastroenterologists and surgeons. The participants were told that the laboratory had noted a substantial increase in trace element testing and the purpose of the questionnaire was to determine the reasons for this increase. Participants were asked about their reasons for requesting serum zinc, copper and selenium levels. Several reply options were provided, as well as space for free text replies. Participants were also asked to describe their type of practice as: conventional, holistic or integrative, anti-ageing medicine or "other".

Additional information about the type of medical practice of the top 24 requestors was obtained from material emanating from the practitioners themselves: the names of the practices, their websites and letterheads.

An estimate of the number of general practitioners in the Auckland region was provided by the Medical Council of New Zealand.

Results

Between 2004 and 2008 the annual number of trace element test requests increased by 3.5-fold (Table 1). The increase was largely due to a 2.8-fold increase in serum copper, a 3.8-fold increase in serum zinc, and a 3.4-fold increase in serum selenium tests.

Table 1. Trace element tests performed annually (year periods begin on 1 September of each year). Blood mercury testing was introduced in 2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Serum copper</th>
<th>Urine copper</th>
<th>Serum zinc</th>
<th>Blood mercury</th>
<th>Urine mercury</th>
<th>Serum selenium</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004–2005</td>
<td>794</td>
<td>119</td>
<td>2082</td>
<td>0</td>
<td>62</td>
<td>242</td>
<td>3299</td>
</tr>
<tr>
<td>2005–2006</td>
<td>1089</td>
<td>101</td>
<td>2922</td>
<td>77</td>
<td>72</td>
<td>314</td>
<td>4575</td>
</tr>
<tr>
<td>2006–2007</td>
<td>1763</td>
<td>101</td>
<td>5069</td>
<td>275</td>
<td>72</td>
<td>932</td>
<td>8212</td>
</tr>
<tr>
<td>2007–2008</td>
<td>2223</td>
<td>84</td>
<td>7826</td>
<td>375</td>
<td>86</td>
<td>821</td>
<td>11415</td>
</tr>
</tbody>
</table>

The distribution of test requests was markedly skewed, with a relatively small number of requestors being responsible for the majority of requests. The top 27 requestors comprised 21 general practitioners, 2 surgeons, one gastroenterologist, one psychiatrist, one paediatrician and one pain specialist. The surgeons and gastroenterologist were excluded from the "frequent requestor" outlier group because...
their patients are likely to have malabsorption or parenteral nutrition in whom trace element tests are appropriate. The remaining 24 requestors are referred to as the "top 24".

Figures 1–4 show that the number of tests ordered by the top 24 increased markedly between 2004 and 2008. In the 2007-2008 year, the top 24 requestors were responsible for ordering 55% of serum copper, 61% of serum zinc, 63% of serum selenium and 66% of blood mercury tests.

Although responsible for ordering the majority of trace element tests, these 24 medical practitioners represent only approximately 1.5% of the 1566 GPs practising in the Auckland region.

The distribution of serum zinc results of patients from the top 3 zinc requestors was not different from that expected for a normal population, with few results outside the reference interval (Figure 5). The distribution showed a 2.5th percentile of 9.1 µmol/L, which is very similar to a healthy US population from the NHANES II study, where the 2.5th percentiles for non-fasting serum zinc were 9.0 µmol/L in females and 9.3 µmol/L in males.¹

The distribution of all serum zinc results requested during that year was similar, except for a larger tail of low serum zinc results (Figure 5). Analysis of these low serum zinc results indicated that they largely represent patients with hypoproteinemia and/or gastrointestinal disorders, many of whom were hospitalised.

Figure 1. Serum copper tests performed during the study period

![Serum copper tests performed during the study period](image-url)
Figure 2. Serum zinc tests performed during the study period

![Serum Zinc Tests Graph]

Figure 3. Serum selenium tests performed during the study period

![Serum Selenium Tests Graph]
Figure 4. Whole-blood mercury tests performed during the study period. The test was introduced during the 2005-6 year.

Figure 5. Distribution of serum zinc levels in patients from the top 3 requestors (dotted line) compared with all patients (solid lines), for the 2007-2008 year of the study. Vertical dotted lines show the reference interval.
Figure 6. Distribution of serum selenium levels in patients from the top 3 requestors (dotted line) compared with all patients (solid lines), for the 2007-2008 year of the study. Vertical dotted lines show the reference interval.

The distribution of serum selenium results of patients from the top 3 selenium requestors showed few results outside the reference interval (fig. 6). Low selenium results were largely found in hospitalised patients and in requests from gastroenterologists. There was a long tail of high serum selenium results (>2.0 umol/L) which is likely to represent people on selenium supplements.

The distribution of serum copper and whole blood mercury results of patients from the top 3 requestors of these tests were not different from that expected for a healthy population, with few results outside the reference interval, and also did not differ from the distribution of results from all requestors (data available on request).

**Questionnaire**—Of the 24 requestors who were sent the questionnaire, 15 responded. Tables 1 and 2 show the percentage of the 15 respondents giving the indicated responses.
Table 2. Responses to the questionnaire

<table>
<thead>
<tr>
<th>Reasons for requesting serum zinc</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc deficiency is common in New Zealand</td>
<td>67%</td>
</tr>
<tr>
<td>Zinc deficiency is a common cause of depression</td>
<td>13%</td>
</tr>
<tr>
<td>Zinc deficiency is associated with low immune function</td>
<td>67%</td>
</tr>
<tr>
<td>To see if zinc supplements are required</td>
<td>47%</td>
</tr>
<tr>
<td>To monitor the patient’s use of zinc supplements</td>
<td>33%</td>
</tr>
<tr>
<td>To enable calculation of the zinc/copper ratio</td>
<td>27%</td>
</tr>
<tr>
<td>To optimise my patient’s health and not necessarily to detect deficiency or toxicity</td>
<td>27%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for requesting serum copper</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc/copper ratio is useful</td>
<td>33%</td>
</tr>
<tr>
<td>To test for Wilson’s disease</td>
<td>13%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for requesting serum selenium</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium deficiency is common</td>
<td>40%</td>
</tr>
<tr>
<td>Selenium supplementation will/may reduce the incidence of certain cancers</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of practice (self-described)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional general practice</td>
<td>33%</td>
</tr>
<tr>
<td>Holistic or integrative or alternative medical practice</td>
<td>27%</td>
</tr>
<tr>
<td>Anti-aging medicine</td>
<td>13%</td>
</tr>
<tr>
<td>Interest in autism/ADHD</td>
<td>20%</td>
</tr>
</tbody>
</table>

The most common reasons for serum zinc testing cited by the questionnaire respondents were the notions that zinc deficiency is common in New Zealand and that this is associated with low immune function. Consistent with this, the use of zinc supplements appears to be common among this group of practitioners. The belief that the serum zinc/copper ratio is clinically useful was expressed by a third of the respondents. None of the respondents cited gastrointestinal disease or parenteral nutrition as reasons for testing trace elements.

Additional information on the type of medical practice was obtained from the practitioners’ websites and letterheads. Thirteen of the top 24 requestors (54%) described themselves as practising holistic, integrative, anti-ageing, complementary, or anthroposophic forms of medicine, chelation therapy, Mind-Body medicine, or “bio-identical” hormone therapy. Two others described themselves as having a special interest in "biomedical" treatments for autism.

Discussion

Our findings show a marked increase in laboratory testing for the trace elements zinc, copper, selenium and mercury from 2004 to 2008. To understand the reasons for this increase, and because of concern that it might reflect inappropriate laboratory test requesting practice, we analysed the distribution of test requests and sent a questionnaire to the most frequent requestors.

The main findings were (a) that the majority of the increase was attributable to a small number of requestors, and (b) that the requestors were largely identified with unconventional (alternative) types of medical practice.

A belief that zinc deficiency is common in the general population of New Zealand appears to be the reason for the majority of serum zinc tests. It seems likely that the serum zinc level may be used as an indicator of the need for zinc supplements. Is
there any evidence that zinc deficiency is common in this population, or that routine serum zinc measurements are justified?

Zinc balance in humans is maintained by a homeostatic mechanism which regulates its absorption and excretion.\(^2,3\) When dietary zinc intake is low, zinc absorption can increase to nearly 100%, while urinary and faecal excretion fall to low levels.\(^4\) This adaptation allows zinc balance to be maintained with zinc intakes as low as 2–3 mg/day.\(^5-7\)

Zinc deficiency occurs when this homeostatic mechanism fails. This may occur in patients with malabsorption or chronic diarrhoea, if total parenteral nutrition (TPN) is given without adequate zinc supplementation, in malnutrition or eating disorders, in patients receiving chelation therapy (e.g. for iron overload) and in acrodermatitis enteropathica, a rare inherited defect of intestinal zinc transport.\(^2,8\) Severe zinc deficiency is associated with stunted growth, decreased immunity, skin lesions and poor wound healing.\(^9,10\)

Since a wide range of foods including meat, fish, shellfish, nuts, seeds, legumes and whole-grain cereals are rich in zinc,\(^10\) deficiency does not occur in people who consume a balanced diet and have normal gastrointestinal function. Vegetarians may be theoretically more likely to become deficient because zinc from plant sources is less bioavailable due to the presence of phytic acid which inhibits its absorption.\(^11\)

However in practice serum zinc levels are similar in vegetarians and nonvegetarians, and adverse effects from zinc deficiency have not been demonstrated in vegetarians in developed countries.\(^11\) In a survey of risk of zinc deficiency at the population level, New Zealand is classified as a low risk country.\(^9\)

A separate but related question concerns the utility of serum zinc concentration as an index of zinc status. Plasma zinc falls in severe zinc deficiency but it is a poor marker of marginal zinc deficiency.\(^1,12\) During experimental zinc depletion, serum zinc concentrations do not fall consistently unless the zinc intake is below 3 mg/day.\(^13\) The utility of serum zinc measurements is further compromised because the serum zinc level is influenced by other factors unrelated to zinc status. As serum zinc is 98% protein-bound, zinc levels are low in hypoproteinaemic patients, without indicating zinc deficiency.\(^14\) In addition, the proteins to which zinc is bound (albumin and alpha-2 macroglobulin) are negative acute phase reactants: their concentrations decrease in response to inflammation.\(^1\) For this reason low serum zinc is a non-specific finding in a variety of disease states and does not indicate zinc deficiency in these settings.\(^15,16\)

The notion that the serum copper/zinc ratio is clinically useful appears to be the reason for the increase in copper requests. An increase in the copper/zinc ratio has been reported in numerous disease states.\(^15,17-21\) The increase in the serum copper/zinc ratio in many diseases occurs because serum copper has a positive acute phase response (increases) and serum zinc has a negative acute phase response (decreases) in inflammatory states. Thus the serum copper/zinc ratio has no diagnostic value other than as a non-specific marker of disease.

Plasma zinc levels are often low in major depression, and there is evidence that this may be due to activation of an inflammatory response in this disorder.\(^16,22\) There is no convincing evidence that zinc deficiency is associated with depression, or that measuring serum zinc is of any benefit to these patients.
A large number of zinc, copper and mercury tests are requested on children with autism spectrum disorder. The belief that biochemical imbalances including trace elements are the cause of autism, and that their correction by means of supplements and/or chelation therapy can be used to treat the disorder, is known as the "Biomedical approach" to autism. This approach has been thoroughly discredited, and there is no convincing evidence for any trace element imbalance in autism. Current guidelines for the investigation of autism spectrum disorder do not include the measurement of trace elements.

Prior to 1990 the selenium status in the New Zealand population, especially in the South Island, was low due to the low selenium content of our soils, but has since improved, while remaining lower than some countries. However, clinically significant selenium deficiency has not been found in the general population of New Zealand, and is confined to patients with malnutrition or malabsorption.

Epidemiological studies which demonstrated an association between low serum selenium levels and increased incidence of some cancers and mortality as well as an early randomised controlled trial suggested that selenium supplements could reduce the incidence of prostate and other cancers. This led to a major randomised controlled trial which has conclusively shown that selenium supplementation does not produce any reduction in prostate cancer or cancer of any type.

The reasons for requesting blood mercury tests were not examined in the questionnaire. However, information provided on the request forms, written information emanating from the practitioners, as well as communications between one of the authors (J.D.) and the requestors suggests that the main reasons were a belief that mercury toxicity, particularly due to amalgam dental fillings, is an important cause of fatigue, cognitive decline, memory loss, Alzheimer's disease, depression and autism. In fact there is no convincing evidence that mercury has any causal relationship to any of these conditions.

The marked increase in trace element testing in Auckland mirrors the growth in use of dietary supplements and alternative / complementary medicine in New Zealand and reflects the type of medical practice of the most frequent trace element test requestors. The majority of zinc, copper, selenium and mercury tests are requested for reasons which are not evidence-based. The inappropriate laboratory testing of trace elements represents a significant waste of public sector health care resources. The unit costs of trace element tests in this laboratory ranged from NZ$26 for serum zinc to NZ$49 for whole blood mercury. This suggests that laboratories could achieve significant savings in expenditure by clearly defining appropriate indications for performing trace element tests.

Competing interests: None.

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References:


