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Trace elements in hemodialysis patients: a systematic review and meta-analysis

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Abstract

Background: Hemodialysis patients are at risk for deficiency of essential trace elements and excess of toxic trace elements, both of which can affect health. We conducted a systematic review to summarize existing literature on trace element status in hemodialysis patients.

Methods: All studies which reported relevant data for chronic hemodialysis patients and a healthy control population were eligible, regardless of language or publication status. We included studies which measured at least one of the following elements in whole blood, serum, or plasma: antimony, arsenic, boron, cadmium, chromium, cobalt, copper, fluorine, iodine, lead, manganese, mercury, molybdenum, nickel, selenium, tellurium, thallium, vanadium, and zinc. We calculated differences between hemodialysis patients and controls using the differences in mean trace element level, divided by the pooled standard deviation.

Results: We identified 128 eligible studies. Available data suggested that levels of cadmium, chromium, copper, lead, and vanadium were higher and that levels of selenium, zinc and manganese were lower in hemodialysis patients, compared with controls. Pooled standard mean differences exceeded 0.8 standard deviation units (a large difference) higher than controls for cadmium, chromium, vanadium, and lower than controls for selenium, zinc, and manganese. No studies reported data on antimony, iodine, tellurium, and thallium concentrations.

Conclusion: Average blood levels of biologically important trace elements were substantially different in hemodialysis patients, compared with healthy controls. Since both deficiency and excess of trace elements are potentially harmful yet amenable to therapy, the hypothesis that trace element status influences the risk of adverse clinical outcomes is worthy of investigation.

Background

Hemodialysis is the most common form of treatment for end-stage renal disease (ESRD), and is associated with considerable morbidity and mortality due to accelerated cardiovascular disease and infection. Despite the well-documented burden of disease, much remains to be learned about how best to prevent these complications of hemodialysis.

Hemodialysis removes uremic toxins primarily by allowing equilibration of plasma and dialysate across a semi-permeable membrane. Dialysate is created by adding carefully regulated quantities of biologically essential ions such as potassium, sodium, bicarbonate, and calcium to water that has been treated to reduce solutes to very low levels. The dialysate concentration of other substances such as trace elements is not routinely manipulated. Substances that have lower concentrations in dialysate than in blood tend to be removed by dialysis. Although this is appropriate in the case of uremic toxins, it may lead to depletion of biologically essential substances. Besides the potential for ongoing removal of trace elements by dialysis, hemodialysis patients are at risk for low dietary intake of such substances due to uremia-related anorexia and dietary restrictions.

Hemodialysis patients are exposed to very high volumes (>300 liters/week) of dialysate. Therefore, even minute levels of toxic substances in source water could lead to tiny concentration gradients between blood and dialysate, which in turn could lead to clinically relevant toxicity. Substances present in dialysate but not in blood will tend to accumulate in the patient, and the lack of renal clearance in hemodialysis patients might theoretically lead to toxicity of ingested trace elements even when they are not present in dialysate. Thus, hemodialysis patients are at theoretical risk for both deficiency and accumulation of trace elements, depending on dietary intake, removal by dialysis, the composition of the source water used for hemodialysis, and residual kidney function [1-3].

Deficiency of essential trace elements (such as zinc or selenium) and excess of potentially harmful trace elements (such as lead or arsenic) are both known to have adverse consequences in the general population [4-10]. Although not established, it is plausible that disordered trace element nutritional status (if present) would contribute to morbidity and mortality among hemodialysis patients as well. However, the incidence of abnormal trace element status in dialysis patients has not been comprehensively studied. We performed a systematic review to compare trace element status between hemodialysis patients and healthy controls.

Methods

Data sources and searches

This systematic review is reported according to published guidelines [11]. An expert librarian conducted a comprehensive search to identify all relevant studies regardless of language or publication status. Three electronic databases, MEDLINE (1966 to 13 April 2008), EMBASE (1988 to 13 April 2008), and the Cochrane Library (13 April 2008) were searched. The detailed search strategies are included in Additional file 1. A subject specialist and a methodologist screened each citation or abstract. Any study considered potentially relevant by at least one reviewer was retrieved for further review.

Study selection

The full text of each potentially relevant study was independently assessed by two reviewers for inclusion in the review using predetermined eligibility criteria on a pre-printed form. Studies were eligible for inclusion if they measured trace element concentrations in both a chronic hemodialysis population and a healthy control population. We selected the following trace elements for study *a priori* based on their known or suspected potential to influence health, and after consideration of existing standards for hemodialysis water quality [12]: antimony, arsenic, boron, cadmium, chromium, cobalt, copper, fluorine, iodine, lead, manganese, mercury, molybdenum, nickel, selenium, tellurium, thallium, vanadium, and zinc. Only studies that measured trace element status in whole blood, serum, or plasma were included. Disagreements were resolved by discussion and consultation with a third party. Disagreements arose with 6% of the articles ($\kappa = 0.88$).

Data extraction and quality assessment

We assessed and reported the study quality of included studies using the Downs and Black checklist [13]. Two reviewers independently assessed each included study, and resolved disagreements with the aid of a third party through consensus. An average of 18% of disagreements on quality items occurred. Study characteristics and data of interest were pre-specified, and were recorded in a purpose-built database. One reviewer extracted the data. A second reviewer checked the data for accuracy.

Data synthesis and analysis

We analyzed data using Review Manager 4.2.10 (Oxford, UK) and Stata 10.0 (College Station, Texas, USA). We calculated standardized mean differences (SMD) [14]; the hemodialysis population mean minus the control population mean divided by their pooled standard deviation (SD). By presenting the differences in means relative to variability, we removed the heterogeneous effects of both

unit and assay, with SMD of 0.2, 0.5, and 0.8 units of SD representing small, medium, and large sizes of effect, respectively [15]. One study [16] reported geometric means rather than arithmetic means, requiring us to standardize the differences in log means rather than the differences in mean [17].

We assessed heterogeneity using the I^2 statistic [18,19], and found considerable between-study heterogeneity ($I^2 > 85\%$). Therefore, the primary method of pooling data across studies used a qualitative approach (vote counting [20]; used to tally the number of studies finding that the level of a particular trace element was lower or higher in hemodialysis patients than in controls). We used the sign test to determine whether the vote count tally was statistically significant (provided that there were at least three studies which reported results for the element in question). To provide guidance on the relative magnitude of the differences between hemodialysis patients and controls, we also report random-effects estimates of the pooled SMD for elements where the sign test indicated that levels were significantly different between these two populations. Given the presence of large heterogeneity, we did not formally assess for the presence of publication bias [21].

Statistical sources of heterogeneity were explored using weighted least squares meta-regression [22]. The following study-level variables were considered: sample source (whole blood, serum, plasma), mean duration of hemodialysis treatment (in months), continent on which the study was performed (Americas/Europe versus other) and measurement technique (absorption spectroscopy versus other). The effect of sample size was also explored given the tendency for SDs to be underestimated [23], and therefore SMDs overestimated, when sample sizes are small ($N < 30$).

Results

Search yield

From 1,481 identified citations and abstracts, 226 full articles were retrieved for detailed evaluation (Figure 1). Of these, 128 studies [2,16,24-149] reported relevant data and were included in this review. Most studies were conducted in Europe (47%), Asia (30%), and North America (14%). Seventy-four percent of data came from cross-sectional studies; the remaining data from baseline assessments of randomized controlled trials and prospective cohort studies. Most studies used absorption spectroscopy, emission spectroscopy or neutron activation to measure trace element levels in biological specimens (Additional file 2). Multiple variants of absorption spectroscopy were used.

Populations studied

Sample sizes of hemodialysis patients ranged from 6 to 456 (median 24; Additional file 2). Mean ages ranged from 32 to 74 and percent male ranged from 0% to 100%. Little information was reported on the primary cause of ESRD, co-morbidities, or membrane properties. Control group sample sizes ranged from 5 to 490 (median 28). Mean ages ranged from 28 to 74 and percent male ranged from 0% to 100%. Hospital or laboratory staff (13%), blood donors (7%), non-renal patients (6%), or people drawn from the general population in the same geographic region (6%) were the most commonly specified source populations for control groups. Results of quality assessment are reported in Additional file 2. Time spent on dialysis (39%), description of control participants (29%), and eligibility criteria (20%) were poorly reported. Adjustment or matching for age and sex was infrequent (20%). Technique was well reported (98%), but consideration for measurement error was poor (34%).

Trace element status

Data were available for arsenic, boron, cadmium, chromium, cobalt, copper, fluorine, lead manganese, mercury, molybdenum, nickel, selenium, vanadium, and zinc. The pooled results comparing trace element status for hemodialysis patients with controls are presented in Table 1 and Figure 2. Results stratified by sample source (whole blood, serum, or plasma), or repeated using a fixed-effect model were consistent (data not shown). Available data suggested that levels of cadmium, chromium, copper, lead, and vanadium were higher and that levels of manganese, selenium, and zinc were lower in hemodialysis patients, compared with controls (Table 2). The magnitude of these differences was large (>0.8 SD units) for cadmium, chromium, vanadium, selenium, zinc, and manganese.

Available data for arsenic, boron, cobalt, fluorine, mercury, molybdenum, and nickel were either too limited or too heterogeneous to report. No studies reported data on antimony, fluorine, iodine, tellurium, and thallium.

Meta-regression

We attempted to identify potential explanations for the observed between-study heterogeneity using meta-regression. None of the characteristics considered (sample source, duration of hemodialysis treatment, continent on which the study was performed, or measurement technique) significantly modified the association between hemodialysis treatment and the blood levels of the trace elements studied (data not shown).

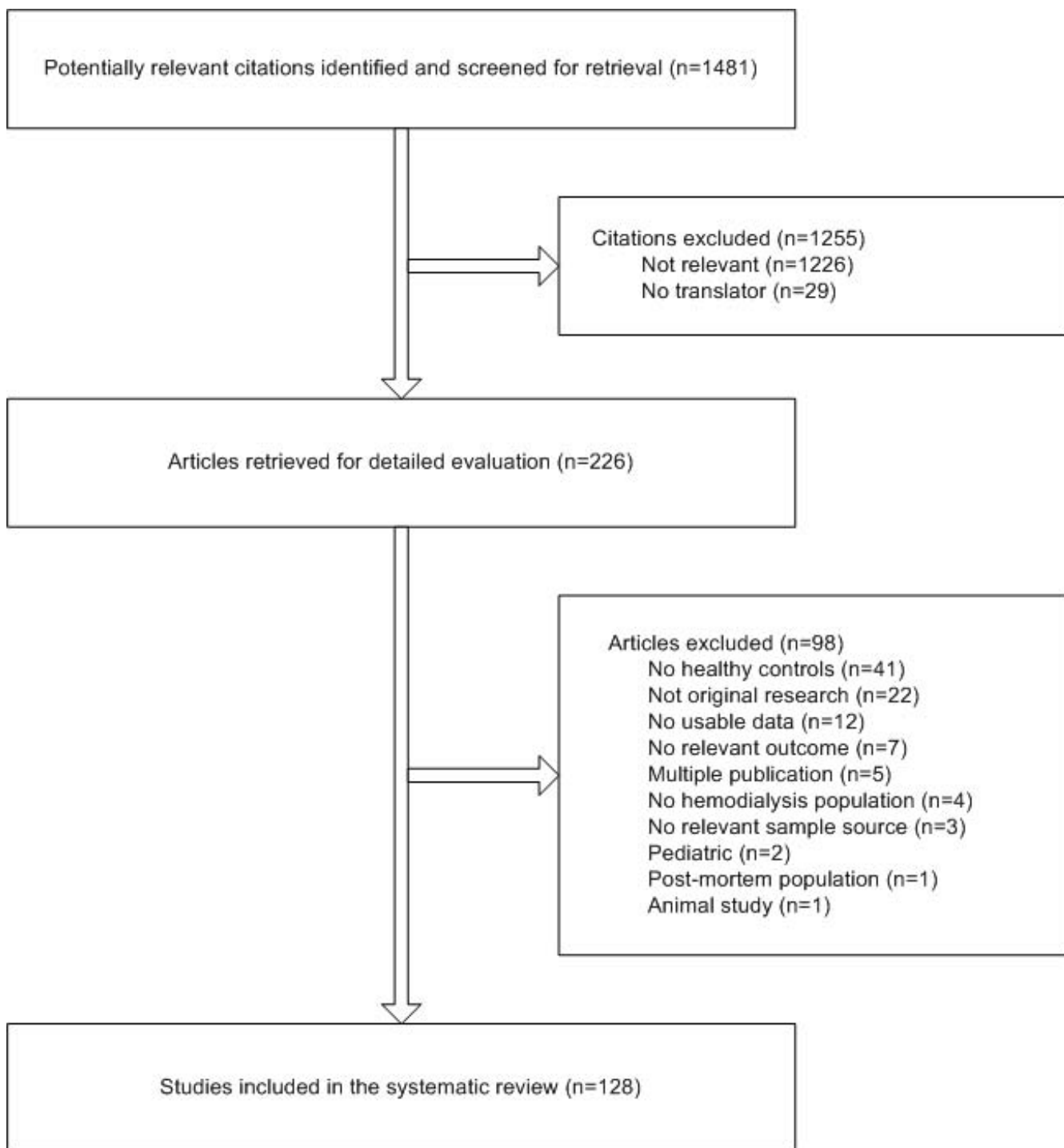


Figure 1
Flow diagram of study selection.

Discussion

We found that hemodialysis patients appear to have lower levels of zinc and selenium than people in the general population. Zinc deficiency is a leading cause of disease in developing countries [4], and is associated with delayed wound healing [5], and immune deficiency characterized

by impaired cell proliferation, abnormal T-cell function, defective phagocytosis, and abnormal cytokine expression [150,151], all of which might contribute to the excess risk of infection observed in hemodialysis patients [152-157]. Zinc deficiency may also cause or contribute to a number of relatively non-specific conditions commonly observed

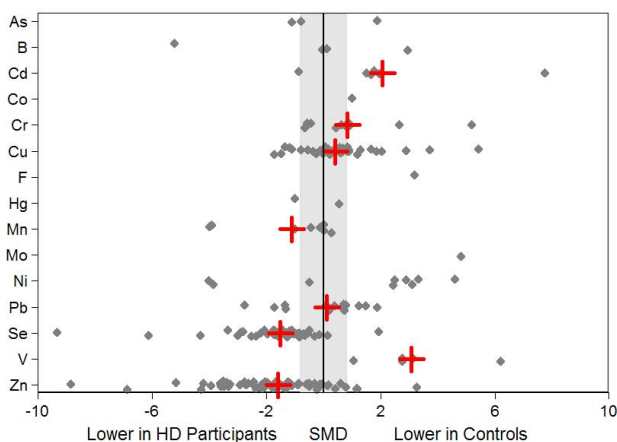


Figure 2
Standardized mean differences of trace element concentrations: hemodialysis participants versus healthy controls. The small solid gray diamonds represent the standardized mean difference (SMD) in trace element concentrations between hemodialysis patients and controls (for each individual study). The large red crosses represent the random-effects pooled SMDs. Results were pooled only for trace elements that were measured in at least three studies and for which the sign test was statistically significant. The shaded gray region denotes SMD representing differences between hemodialysis patients and controls, which are moderate or small (<0.8 standard deviation). Data points outside the gray region represent large differences between hemodialysis patients and controls ($SMD \geq 0.8$ standard deviation).

in hemodialysis patients, including anorexia [158], dysgeusia [159], and impaired cognitive function [160].

Although the biological significance of low blood selenium concentrations is less clear, severe selenium deficiency leads to sudden death and cardiomyopathy in the general population [6,7,161]. Lower levels of serum selenium without severe deficiency have been associated with hypertension [162], heart failure [163,164], and coronary disease [165] in the general population, and with cardiomyopathy among dialysis patients [1,166,167]. Finally, mild selenium deficiency appears to increase susceptibility to oxidant stress [168,169], which may be relevant to hemodialysis patients in whom oxidative stress is markedly increased [170-172].

In addition to the lower levels of selenium and zinc, hemodialysis patients seem to have higher average levels of certain trace elements compared with healthy controls. It was not possible to compare absolute levels of trace elements across studies (given the different techniques and specimens), and therefore we could not estimate the proportion of hemodialysis patients who have trace element

levels in the toxic range. However, for many of the elements, the SMD for the differences between hemodialysis patients and controls exceeded 0.8 SD, which is considered to be a large between-group effect by authorities [15].

For most of the trace elements studied, the biological significance of higher blood levels is unclear. However, excessive levels of lead or arsenic in blood and other tissues are known to be potentially harmful. For example, minor elevations in whole blood lead levels are associated with impaired cognitive function [173,174], impaired hemoglobin synthesis, and hypertension [175,176]. Cerebrovascular disease and renal insufficiency [177-179] also appear to be more frequent at higher levels of blood lead, perhaps mediated by higher blood pressure. Thus, higher blood levels of lead may increase the risk of cardiovascular disease, although the mechanism remains unclear. Similarly, inorganic arsenic causes tissue damage by multiple mechanisms including oxidative injury [180,181], inhibition of DNA repair [182], and chromosomal damage (deletion, aneuploidy [183]), and higher levels of arsenic are associated with increased risk of peripheral vascular disease [184,185]. Animal studies suggest that low selenium status may predispose to arsenic toxicity [186], and underweight or malnourished humans may also be at increased risk [187], suggesting that hemodialysis patients may be at higher than average risk of arsenic toxicity.

Implications of the findings

Although the concentration of some trace elements in hemodialysis source water is monitored annually in accordance with federal regulation [188], blood or body levels of these substances are rarely (if ever) measured in hemodialysis patients. The potential for the accumulation of trace elements to cause harm in hemodialysis patients is exemplified by aluminum. Aluminum toxicity led to serious toxicity (anemia, disabling encephalopathy, neuropathy and severe symptomatic bone disease) in dialysis patients prior to the recognition that aluminum in dialysate and oral medications was responsible [189-193]. It is difficult to overstate the importance of this discovery for nephrology practice, which led to the elimination of aluminum-related toxicity (and substantial improvements in patient outcomes) within a few years. Today, clinically obvious toxicity due to accumulation of aluminum is exceedingly rare in hemodialysis patients, and the existing regulation [188] has been remarkably effective at reducing the risk of acute toxicity from excess trace elements such as fluorine [194-196]. However, the possibility that other trace elements may accumulate in patients with kidney failure and cause unrecognized chronic toxicity has received surprisingly little attention.

Oral trace element supplements are readily available, and oral zinc and selenium preparations have been shown to

Table 1: Trace element concentrations independent of sample source

Element	Number of cohorts ^b	Number of hemodialysis participants and control participants	Pooled ^a SMD	I ² , %	Range of SMDs	Number of studies significantly favouring lower concentrations in hemodialysis participants	Number of studies significantly favouring lower concentrations in control participants	Number of studies with non-significant findings
Arsenic	3	110/54	-	96	(-1.23, 1.77)	1	1	1
Boron	4	69/494	-	96	(-5.21, 2.96)	1	1	2
Cadmium	6	722/968	2.07	98	(-1.01, 7.7)	1	5 ^c	0
Chromium	11	330/635	0.84	95	(-0.66, 5.14)	0	6 ^c	5
Cobalt	1	7/9	-	-	-	0	0	1
Copper	42	1712/1444	0.52	93	(-1.74, 5.28)	6	16 ^c	20
Fluorine	1	7/8	-	-	-	0	1	0
Lead	14	1217/1751	0.11	96	(-2.89, 1.73)	4	5 ^c	5
Manganese	8	399/522	-0.7	96	(-3.96, 0.29)	4 ^c	0	4
Mercury	2	607/264	-	99	(-0.94, 0.49)	1	1	0
Molybdenum	1	14/59	-	-	-	0	1	0
Nickel	9	369/323	-	99	(-3.96, 4.67)	3	6	0
Selenium	46	1496/1443	-1.50	91	(-9.16, 1.97)	37 ^c	1	8
Vanadium	5	112/137	3.07	87	(1.18, 6.28)	0	5 ^c	0
Zinc	74	2515/2699	-1.61	95	(-8.99, 3.24)	56 ^c	5	13

^aPooled SMDs using the random-effects method; this estimate indicates the average effect of all included studies. Negative values indicate lower concentrations in the hemodialysis participants and positive values indicate lower concentrations in the control participants. Pooled SMDs are reported only when vote counting results are significant.

^bSome studies counted more than once if results reported by strata, for example, women and men separately.

^cVote counting sign test results were significant at the $P \leq 0.05$ level. Applied to comparisons with a minimum of three studies. SMD = standardized mean difference.

Table 2: Summary of findings

	Probably accumulates in hemodialysis patients	May accumulate in hemodialysis patients	Probably deficient in hemodialysis patients	Insufficient information
Cadmium	X			
Chromium	X			
Nickel	X			
Vanadium	X			
Copper		X		
Lead		X		
Manganese			X	
Selenium			X	
Zinc			X	
Antimony				X
Arsenic				X
Boron				X
Cobalt				X
Fluorine				X
Iodine				X
Mercury				X
Molybdenum				X
Tellurium				X
Thallium				X

increase blood levels of these elements in dialysis patients [197-200]. However, few data describe the impact of trace element supplementation on clinical outcomes in hemodialysis patients, despite the fact that correction of zinc deficiency is beneficial in the general population [5,201-204], including significantly reducing the risk of infection and all-cause death [205-211]. Data examining the relation between trace element status and clinical outcomes in hemodialysis patients are similarly scarce. One relatively small ($N = 265$) study published in the Lithuanian language shows a significant association between lower plasma zinc levels and the risk of infection [212]. Our data suggest that future studies should investigate the link between zinc or selenium status and clinical outcomes in dialysis patients, in whom the risk of infection is dramatically elevated compared with people with normal kidney function [152-157].

Limitations

The available literature has several potentially important limitations. First, study quality was moderate to poor, and many of the studies were relatively small. Second, the available data include multiple different analytical techniques, study populations, control groups, and specimen types (whole blood, serum, plasma). Perhaps for this reason, there was substantial between-study heterogeneity in the results, meaning that the extent to which trace element levels are higher or lower in hemodialysis patients cannot be estimated with certainty. We were unable to identify statistical sources of this heterogeneity, perhaps because we only had access to study-level (rather than patient-level) data. Despite the heterogeneity, for several of the elements studied, the great majority of studies found differences between hemodialysis patients and controls. Since the same technique and specimen types were used for both patients and controls, it is unlikely that these differences are spurious. However, it remains possible that important differences exist for other substances known or suspected to influence health. Third, studies generally did not report data on dietary intake of trace elements and thus we cannot assess whether reduced consumption of foods containing zinc and selenium was responsible for the lower levels of these elements among hemodialysis patients. Fourth, although we found large differences between the blood levels of certain trace elements in hemodialysis patients and those in control participants, the clinical significance of this finding remains to be confirmed. Fifth, although we studied blood levels of trace elements, it is possible that bone or other compartments may better reflect trace element body status, especially for heavy metals such as lead [213]. Sixth, although simultaneous derangement of multiple trace elements (for example, low selenium and excess arsenic) may have synergistic

toxicity [186], the nature of the available data precluded us from determining how frequently this occurs in hemodialysis patients. Finally, although all systematic reviews have potential limitations, we conducted and reported this analysis according to published guidelines aimed at reducing bias [11]. Nonetheless, as with all systematic reviews, the strength of our conclusions is influenced by the quality of the studies on which they are based.

Conclusion

In summary, we found that average blood concentrations of biologically important trace elements were substantially different in hemodialysis patients, compared with healthy controls. Since both deficiency and excess of trace elements are potentially amenable to therapy, the hypothesis that trace element status influences the risk of adverse clinical outcomes appears worthy of investigation, especially when one considers the experience of the nephrology community with aluminum.

Abbreviations

ESRD: end-stage renal disease; SD: standard deviation; SMD: standard mean differences

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MT contributed to the conception and design, study selection, interpretation of data, and drafted the manuscript. NW managed the project, contributed to the conception and design, managed the acquisition of data (study selection, quality assessment, data extraction), conducted the analysis, and contributed to the drafting of the manuscript. BH, SK, CF, BM, RT, and JG contributed to the conception and design, interpretation of data, and revised the manuscript critically for important intellectual content. All authors approved the final manuscript.

Additional material

Additional file 1

Appendix. Literature search strategies.

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Additional file 2

Appendix Table S1 and S2. Table S1 – Description of included studies.

Table S2 – Quality assessment of included studies.

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