kidney and dialysis

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Review

Trace Elements and Their Management in Dialysis Patients—Pathophysiology and Clinical Manifestations

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Abstract: Recently, as the number of elderly dialysis patients has been increasing, complications associated with low nutritional status such as infectious disease have had a strong influence on the prognosis of dialysis patients. Nutritional disorders are caused by the inadequate intake of the three major nutrients—proteins, fats, and carbohydrates—as well as vitamin and mineral deficiencies. Minerals are composed of various elements, including small-amount elements and trace elements, which are present in the human body in very small quantities lower than that of iron. In dialysis and predialysis patients, zinc, manganese, and selenium are the three major elements that are significantly depleted as compared to normal subjects; these deficiencies are sometimes symptomatic. Zinc deficiency is manifest as anemia, taste abnormality, and delayed wound healing, while selenium deficiency is associated with impaired cardiac function and immunocompromised condition. Zinc has multiple functions, since various enzymes, including DNA polymerase and RNA polymerase, need zinc as a cofactor, while selenium is a component of selenoproteins, including glutathione peroxidase and thioredoxin reductases, which are major antioxidative stress enzymes. These elements can only be supplemented exogenously and contribute to the sustainable QOL of dialysis patients. On the other hand, as regards other trace elements, including copper, chromium, manganese, lead, arsenic, etc., the association of their deficiency or intoxication with various involvements of dialysis patients were investigated, although all investigations were performed in cross-sectional studies or observational studies. Therefore, the supplementation of these elements is inconclusive, given the scarcity of other intervention studies. More conclusive studies are endorsed for the establishment of proper supplementation strategies.

Keywords: trace elements; dialysis; zinc; selenium

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1. Introduction

In recent years, the concept of nutritional management for dialysis patients has been changing, and the number of elderly dialysis patients has been increasing. This is due to the fact that the complications associated with low nutritional status, such as sarcopenia and frailty, have a strong influence on the prognosis of dialysis patients, and concerns about nutritional disorders caused by excessive dietary restriction have become apparent. Nutritional disorders are caused by the inadequate intake of the three major nutrients—proteins, fats, and carbohydrates—as well as vitamin and mineral deficiencies, which cannot be ignored. In this article, we focus on trace elements among minerals, especially zinc and selenium, which have attracted considerable attention in recent years.

2. What Are Trace Elements?

There are currently 118 known elements on earth, and all substances and objects are composed of these elements. The human body is also composed of various elements. In terms of its composition, 60% of the human body is water (H_2O), with the largest content of oxygen, which makes up 90% of the body. Next is C, which makes up organic matter, and H is the third largest by weight, although it is present in large quantities as a molecule

because of its small atomic weight of 1. Next is N, which makes up the amino group of amino acids. O, C, H, and N are called macroelements (Figure 1). The largest elements with smaller amounts are Ca and P, which are constituents of bone, and together, they account for 99% of the human body. In contrast, the term mineral is often confused with element. Mineral comes from "mine" and "mineral mine" and is used as a synonym for metal in ordinary daily life but it is used with a different meaning as a term related to nutrition. In other words, proteins, lipids, and carbohydrates are the three major nutrients, and the remaining two become minerals and vitamins, meaning an inorganic substance, which is a general term for elements other than O, C, H, and N, as pointed out earlier. Among them, Ca, P, S, K, Na, Cl, and Mg are contained in relatively large amounts in living organisms and are called small-amount elements among minerals and measured in clinical practice in blood collection tests. In contrast, minerals with lower contents, i.e., Fe and below, are trace elements: Fe, F, Si, Zn, Mn, Cu, Se, I, and Mo. These small-amount elements are called trace elements, and together, they are referred to as the 16 essential elements of minerals. From a nutritional point of view, minerals are not necessarily metals, such as Fe, Zn, and Cu, i.e., substances that are hard at room temperature and have luster. In addition to these metallic elements, F, Se, and I are minerals, although they are nonmetallic elements.

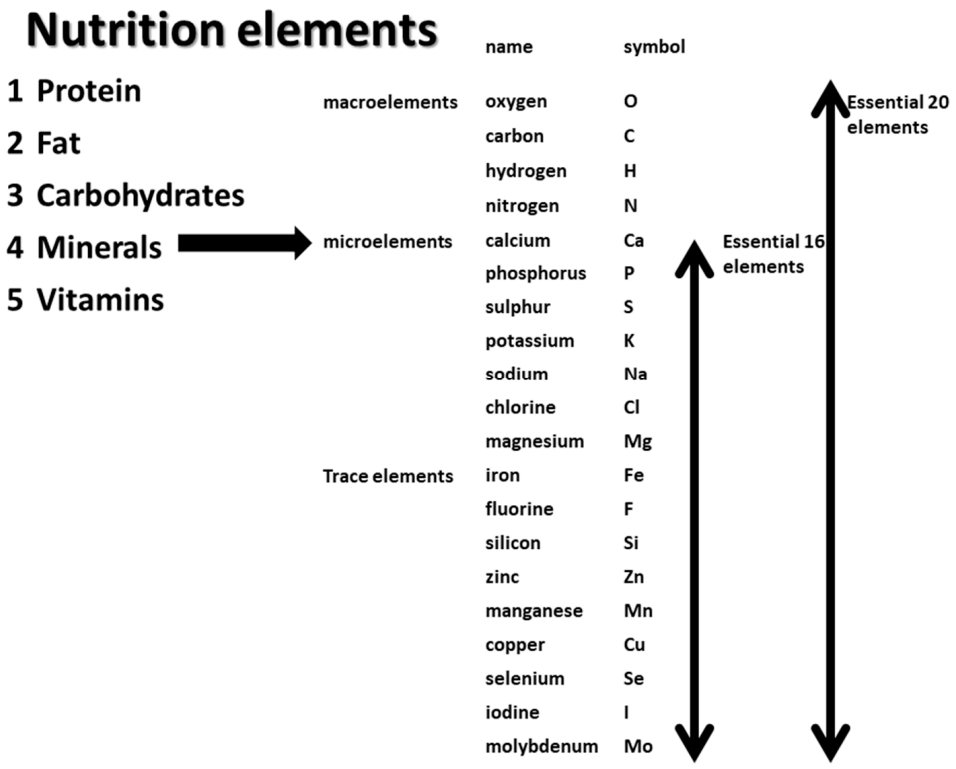

Figure 1. Nutrition elements. Five nutritional elements in which minerals are included. Minerals comprise macroelements, microelements, and trace elements.

Trace elements or minerals are important for four reasons. First, they are structural materials that form the bones and teeth; Ca, P, and Mg are known to make up bones, and F makes up teeth. Secondly, they are activators of enzymes in the body; Zn, Mn, Cu, Mg, and Ca are examples of this, and I makes up part of the thyroid hormones. I is part of the thyroid hormones, and some proteins (selenoproteins and heme proteins) are part of functional proteins. Thirdly, Na, K, and Cl are ions in body fluids, both intracellularly and extracellularly, that maintain the function of various organs. Finally, minerals do not contain calories, and they can only be obtained from food because they cannot be synthesized in the body.

3. Deficiency of Trace Elements

The importance of these minerals and trace elements is due to the fact that minerals and trace elements are decreasing in the Earth's soils; data presented at the Earth Summit in Rio de Janeiro in 1992 indicate that the amount of minerals in the world's soils has decreased over the past 100 years. This is probably due to the abuse of chemical fertilizers. As a result, trace elements in soils and crops have been depleted, with the end result that mineral intakes have decreased and requirements are not being met. Apart from dietary intake, deficiency and excess of trace elements are known to occur in renal failure and dialysis. The blood concentrations of trace elements in renal failure, hemodialysis, and peritoneal dialysis patients are higher than those in normal subjects for many trace metals, including Cr, Mo, and Si, and nonessential elements, such as cobalt, Ni, vanadium, strontium, and Cd. This is because these elements are mainly excreted by the kidneys. In contrast, there are some elements that become deficient, the most common of which are zinc and selenium (Table 1).

Table 1. Trace elements and their concentrations in predialysis, hemodialysis, and peritoneal dialysis patients. ↑ represents "higher than normal", ↓ "lower than normal", and → "the same as normal", and ? "no data available".

Trace Element	Normal Range	Predialysis	Hemodialysis	Peritoneal Dialysis	Deficiency Symptoms
Zinc (Zn)	60–121 mg/dL	↓	↓	↓	Growth retardation, wound-healing delay, taste disorder, and sexual dysfunction
Manganese (Mn)	0.31–1.04 mg/dL	↓	↓ or →	→	Anemia and glucose intolerance
Selenium (Se)	18–40 mg/mL	↓	↓	↓	Cardiac dysfunction, immune disorders, and carcinogenesis
Copper (Cu)	68–128 mg/dL	→	→ or ↑	→	Hemolysis, leukocytosis, and metabolic acidosis
Cobalt (Co)	0.04–0.40 mg/L	→	↑	↑	Cardiac dysfunction and impairment of gluconeogenesis
Chromium (Cr)	0.04–0.35 mg/dL	↑	↑	↑	Liver dysfunction, renal dysfunction, and carcinogenesis
Molybdenum (Mo)	0.27–1.17 mg/L	→	↑	?	Amino acid metabolism disorder, arthropathy, and hypercalcemia
Vanadium (V)	0.10–1.0 mg/L	→	↑	?	Bone disease, dyslipidemia, anemia, and hypertension
Silicon (Si)	0.14–0.20 mg/L	↑	↑	↑	Erythema, bone disease, neuropathy, and Wegener granulomatosis
Nickel (Ni)	0.2–0.8 mg/dL	↑	↑	↑	Cardiac ischemia, anemia, and bone disease
Strontium (Sr)	15–30 mg/L	→	↑	↑	Osteomalacia
Bromine (Br)	2.19–5.00 mg/L	→	↑	↑	Sleep disorders
Cadmium (Cd)	2.19–5.00 mg/L	↑	↑	↑	Growth defects, hypertension, and hyperparathyroidism
Rubidium (Rb)	0.095–0.272 mg/L	→	↑	→	Depression and central nervous system dysfunction

4. Zinc Deficiency in Dialysis Patients

4.1. Zinc and Zinc Deficiency

Zn is at the center of the activity of various enzymes and acts as an essential factor in their activity. Zinc is taken up by insulin-secreting beta cells in the pancreas to regulate insulin secretion. It is also a component of retinol-binding protein, which is a protein that transports vitamin A in the blood. It is an activator of enzymes involved in DNA synthesis and RNA synthesis and is therefore involved in cell division. Therefore, it is involved in wound healing. In recent years, zinc has been attracting attention because of its importance for the maintenance of taste bud cells on the tongue, which detect taste. It is also involved in the synthesis of the male sex hormone, testosterone. Zinc is involved in a wide variety of enzymatic reactions in the body, and Al-p, which is also measured in blood tests, is well-known. RNA polymerase and DNA polymerase are particularly important, as they are involved in DNA replication and transcription and are deeply involved in cell division and cell regeneration. The resulting symptoms of zinc deficiency are manifold. The skin is an important tissue for wound healing, tissue regeneration, and metabolism. Vitamin A is also important, and its deficiency causes dermatitis and stomatitis. Hair root cells also actively divide, and hair loss is observed. The intestinal epithelium is also actively regenerates and divides, and a zinc deficiency causes a loss of appetite. Laboratory findings include low blood zinc levels and low levels of alkaline phosphatase, the enzyme primarily responsible for its activity. Zinc deficiency anemia is also observed. Last year, the Japanese Society of Clinical Nutrition developed diagnostic criteria for zinc deficiency (Figure 2). A suspected case is defined as one in which one or more of the clinical symptoms and low alkaline phosphatase levels are observed, other diseases are ruled out, blood levels are less than 60 μg/dL, and symptoms improve with supplementation [1].

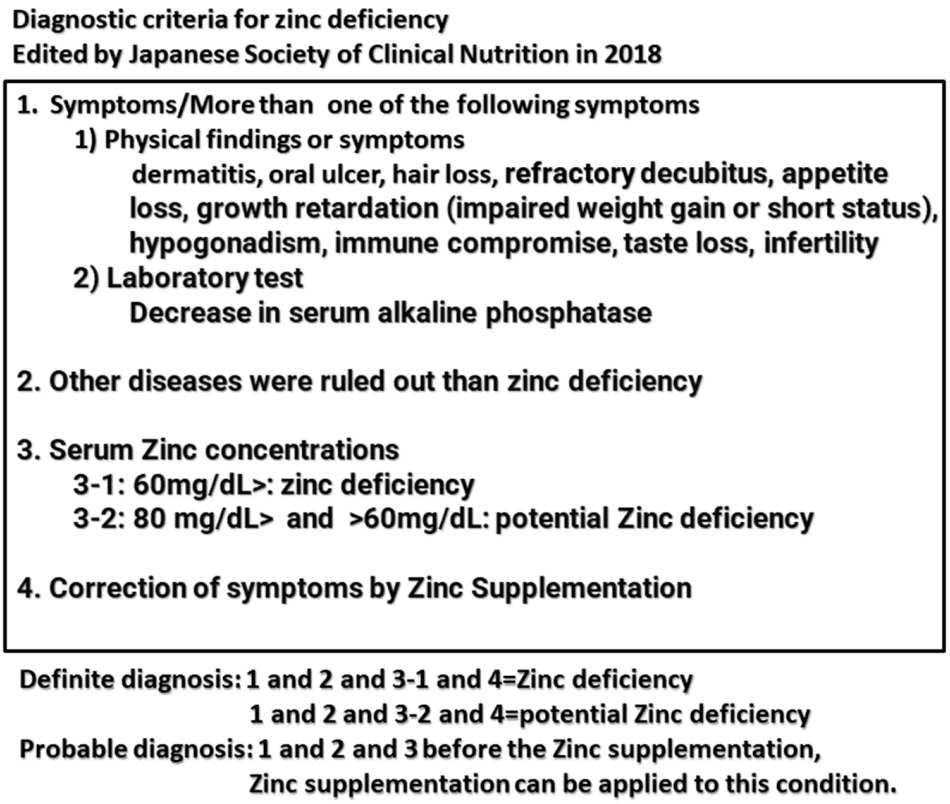

Figure 2. Diagnostic criteria for zinc deficiency. The criteria were edited by the Japanese Society of Clinical Nutrition in 2018 [1]. Reprinted with permission from [1], in 2018 from Hiroko Kodama.

4.2. Zinc Deficiency in Dialysis Patients

Zinc deficiency occurs in a variety of pathological conditions, among which dialysis patients are the most common. The causes of zinc deficiency in dialysis patients are (1) elimination by dialysis, (2) dietary restriction, (3) hypoproteinemia, (4) decreased absorption in the small intestine, (5) increased consumption due to increased oxidative stress, and (6) adsorption by adsorbents and ion exchange resins. It is known that cation exchange resins used for the correction of hyperpotassemia adsorb mineral ions other than K. A 2009 study on the effect of zinc supplementation demonstrated that the serum zinc levels of zinc-supplemented individuals and non-zinc-supplemented individuals were 63.29 ± 9.92 mg/dL and 68.07 ± 12.57 mg/dL, respectively, demonstrating that supplementation improved anemia [2].

Several symptoms associated with anemia in dialysis patients have been documented regarding zinc deficiency. In one study, patients on HD with low serum zinc levels (<65 µg/dL) were randomly assigned to two groups: a polaprezinc group (who received daily polaprezinc containing 34 mg/day of zinc) (n = 35) and a control group (no supplementation) (n = 35) for 12 months. In the polaprezinc group, erythropoiesis-stimulating agent dosage and erythropoiesis resistance (ERI) were significantly decreased at 10 months and 9 months, respectively, as compared with the baseline value. Multiple stepwise regression analysis revealed that the change in the serum zinc level was an independent predictor of lowered ERI. In conclusion, zinc supplementation reduces ERI in patients undergoing HD and may be a novel therapeutic strategy for patients with renal anemia and low serum zinc levels [3]. It has also been reported that Zinc sulfate ameliorates pruritus in patients on maintenance hemodialysis [4]. In the study, a double-blind, randomized, placebo-controlled trial was conducted on 40 adults with end-stage renal disease (ESRD) who were on maintenance hemodialysis. Patients were randomized to receive either zinc sulfate (440 mg/day) or placebo for two consecutive months. The authors reported that zinc sulfate was more effective than the placebo for the relief of pruritus. The main mechanism of this effect is considered to be an inhibitory effect exerted by zinc on histamine release from mast cells. Two other RCTs showed that zinc supplementation was more effective at reducing itching than placebo or hydroxyzine [5,6]. Zinc deficiencies and high serum histamine levels have also been observed in itching patients with ESRD. The sense of taste is also affected by zinc, which plays an important role in the proliferation and maintenance of sensory neuron cells in taste buds in the tongue. The role in the sense of taste has long been recognized among HD patients in non-Asian countries. Two studies examined the effects of Zn replacement on hypogeusia, which refers to diminished sensitivity to detect a specific taste quality or class of compounds [7,8]. In a recent study, the authors divided patients on hemodialysis into two groups based on serum zinc concentration. Salt taste acuity and preference were determined by a sensory test using varying concentrations of NaCl solution, and dietary sodium intake was estimated using 3-day dietary recall surveys. They found that the mean salt recognition threshold and salt taste preference were significantly higher in the zinc-deficient group than in the non-zinc-deficient group. They also reported that there was a significant positive correlation between salt taste preference and dietary sodium intake in the zinc-deficient group. In addition, interdialytic weight gain was significantly higher in the zinc-deficient group than in the non-zinc-deficient group [9]. Finally, Zinc plays an important role in regulating every phase of the wound-healing process, ranging from membrane repair, oxidative stress, coagulation, inflammation, immune defense, tissue re-epithelialization, and angiogenesis to fibrosis/scar formation. Several clinical studies have stressed the importance of zinc in skin ulcer treatment. Although not in the case of dialysis patients, a randomized, double-blind, placebo-controlled trial was conducted regarding the treatment of diabetic foot ulcers [10]. The authors demonstrated that 220 mg zinc sulfate supplementation for 12 weeks had beneficial effects on parameters of ulcer size and metabolic profiles among diabetic foot ulcer patients. A more recent study investigated the relationship between zinc deficiency and clinical outcome in patients with critical limb ischemia [11]. However, in a retrospective observational study of a de novo

infrainguinal bypass grafting operation, the authors found that patients in the Zn deficiency group were more likely to have undergone hemodialysis and that graft patency, limb salvage, amputation-free survival, and complete wound-healing rates were significantly lower in the Zn-deficient group. Finally, another report showed that zinc deficiency is related to mortality in dialysis patients [12]. Zinc plays an important role in immune systems and the treatment and prevention of infectious disease. A clinical study reported that in long-term dialysis patients, the serum level of zinc was an independent predictor of future hospitalization due to infectious diseases and of overall mortality. The authors enrolled 111 patients on maintenance dialysis and measured serum levels of selenium, copper, and zinc. Patients were followed for 2 years or until death or withdrawal. Multivariate Cox regression analysis indicated that zinc deficiency (HR, 0.979; 95% CI, 0.966–0.992; $p = 0.002$) were more likely to be hospitalized for infectious diseases. Multivariate Cox regression also indicated low serum levels of zinc independently predict overall mortality. The survival effects of Zn supplementation are considered to be due to its anti-inflammatory and antioxidative effects. Recently, two meta-analyses including intervention studies conducted in both Western and non-Western countries revealed that Zn replacement results in the reduction in serum CRP levels, as well as MDA concentration, a serum oxidative stress marker [13,14]. More recently, it was demonstrated that Zn sulfate supplementation has favorable effects on CRP, fasting blood glucose, and renal function in Zn-deficient diabetic hemodialysis patients [15].

4.3. Treatment of Zinc Deficiency

A list of these trials is presented in Table 2 [3,15–28]. Zinc preparations such as zinc acetate (Novelzine®) and polaprezinc (Promax®) have been used for zinc supplementation. In Japan, a Zn acetate hydrate tablet containing 50 mg of Zn (Nobelpharma Co., Ltd., Tokyo, Japan) is administered orally after each meal (three times daily) (150 mg/day) for the treatment Zinc deficiency. However, in light of the aging population in recent years, the problem is overwhelmingly one of reduced zinc intake due to dietary restrictions and reduced dietary intake. Therefore, dietary supplementation is the best option. Foods rich in zinc include oysters, pork, and beef. Although these foods contain protein, the dietary intake of the elderly is low, so restricting protein intake because of renal failure is likely to result in a deficiency. Another important issue is that the supplementation dose does not always have effects in clinical practice. Therefore, Zn concentration should be evaluated according to serum protein or albumin concentration, since most Zn is bound to albumin or α2-microglobulin in the blood. In addition, Zn is present in the intracellular space of the whole body. Additional evaluation methods need to be explored.

Table 2. Clinical trials of zinc.

Mode	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	40 dialysis HBV non-responder Zn: *n* = 28 Control: *n* = 12	60 mg zinc aspartate after each dialysis session for 8 weeks	None	HBV antibody formation Titer of HVB antibody	Zn group: 77 ± 2.4 µg/dL Control group: 63 ± 2.1 µg/dL	HBV antibody formation Zn: 6 out of 28 patients Control: 2 out of 12 patients Antibody titer Zn: 0–2364 IE/L Control: 0–1110 IE/L	[16]
HD	Randomized, double-blind, before–after trial *n* = 20 (15 women, 5 men)	Zn: 7.7 pmol zinc sulfate (2200 µg) daily Control: cornstarch placebo capsule daily 90 days	None	Serum Zn concentration PCR (protein catabolic rate)	12.2 µmol/L (80 µg/dL) on day 0 to 15.3 µmol/L (100 µg/dL) on day 90	A significant positive correlation (r = 0.61) between PCR and serum zinc concentrations	[17]
HD	Zn group: 34 zinc-deficient HD patients. Control group: 16 sex- and age-matched normal volunteers	Zn: zinc (20 mg/day) Control: placebo 3 months	None	Levels of Zn malondialdehyde (MDA) osmotic fragility of red blood cells	Zn: 12.5 ± 1.0 to 18.8 ± 3.0 µmol/L Control: from 12.3 ± 1.0 to 12.1 ± 1.4 µmol/L	Increase in Zn concentration; Improvement of osmotic fragility; Decrease in the level of MDA	[18]
HD	Randomized, double-blind, before–after trial	Supplementation of Zn: 7.7 µmol zinc sulfate/day (50 mg elemental zinc/day) Control: cornstarch placebo capsule 90 days	None	Serum zinc, dietary intake, HDL, LDL, and TC	Zn: 0.79 µg/mL to 0.96 µg/mL	Increase in serum total cholesterol and LDL; No change in HDL; Increase in reported energy intake; No change in dietary intake of zinc, cholesterol, total fat, or saturated fat	[19]
HD	*n* = 55 hemodialysis patients (32 men and 23 women)	Zinc supplementation group (*n* = 28): 220 mg zinc sulfate capsule Control group (*n* = 27): placebo capsule (220 mg corn starch) 42 days	None	Serum zinc C-reactive protein levels	Zn group: 57.4 ± 2.4 µg/dL to 88.4 ± 4.8 µg/dL	Decrease in serum C-reactive protein: 13.5 ± 3.8 mg/L to 10.5 +/− 3.5 mg/L	[20]

Table 2. *Cont.*

Mode	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	Double-blind zinc-deficient HD subjects Total: n = 53 (25 female and 28 male)	Zn group (n = 27): 220 mg zinc sulfate (50 mg elemental zinc) Control group (n = 26): starch placebo 42 days	None	Serum concentration of zinc, total cholesterol, HDL and LDL cholesterol, and triglycerides	Zn group: 0.53 ± 0.36 µg/mL to 0.86 µg/mL ± 0.42 µg/mL Control group: 0.52 ± 0.25 µg/mL to 0.64 ± 0.29 µg/mL	Increase in serum total cholesterol, serum LDL, and HDL cholesterol serum triglyceride	[21]
HD	Double-blind, randomized, controlled trial Total: n = 60	Zn group (n = 30): 100 mg/day zinc Control group (n = 30): placebo 2 months	None	Paraoxonase (PON) enzyme activity Lipid profile apolipoprotein AI (Apo-AI) and B (Apo-B) levels	Not measured	No change in serum levels of TC, TG, or LDL or Apo-B levels Increase in serum levels of HDL, Apo-AI, and PON activity	[22]
HD	Double-blind, randomized, clinical trial Total: n = 97 ESRD patients with Zn deficiency	Zn group (n = 50): 50 mg/day Zn Control group (n = 47): placebo 6 weeks	None	Seum Zn Homocysteine (hCys) level	Zn group: 56.9 ± 13.9 to 120.8 ± 26 µg/dL Control group: 60.9 ± 9.8 to 63.9 ± 13.2 µg/dL	Decrease in serum hCys	[23]
HD	Double-blind, randomized, controlled trial 65 HD patients	Group A: placebo Group B: zinc (100 mg/day) 2 months.	None	Serum Zn concentration, total antioxidant capacity (TAC), whole blood glutathione peroxidase (GSH) level, superoxide dismutase (SOD) activity, and malondialdehyde (MDA) level	The levels of serum zinc were increased	Increase in TAC, GSH, and SOD activity Decrease in MDA	[24]
HD	Long-term HD patients with low plasma Zn concentrations (<80 mg/dL)	Zn group (n = 40): daily oral Zn No supplements (n = 25) Control (n = 38): age- and sex-matched healthy individuals 8 weeks	None	Plasma concentrations of Zn and Cu, Cu/Zn ratios, oxidative stress, and proinflammatory cytokines percentages of CD4 and CD19 lymphocytes CD4/CD8 ratios	The levels of serum Zn were increased	Decrease in Cu, Cu/Zn ratios, oxidative stress status, and inflammatory responses Increase in percentages of CD4 and CD19 lymphocytes and CD4/CD8 ratios	[25]

Table 2. *Cont.*

Mode	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	Randomized, double-blind, and placebo-controlled trial 60 HD patients	Supplemented group (n = 30; male/female: 19/11): 100 mg/day elemental Zn Control group (n = 30; male/female: 17/13): placebo 60 days	None	serum zinc serum Leptin anthropometric measurements	Supplemented group: male, 81.7 ± 11 µg/dL to 105.5 ± 18 µg/dL; female, 75.5 ± 11 µg/dL to 106.3 ± 16 µg/dL Control group: male, 85.8 ± 16 µg/dL to 83.6 ± 9.6 µg/dL; female, 80.7 ± 18.8 µg/dL to 86.5 ± 12.7 µg/dL	Decrease in leptin in women; Increase in BMI and body weight in men; Increase in albumin and Hb; Negative association between serum zinc and leptin levels	[26]
HD	Prospective clinical trial study Pediatric HD patients between 5 and 18 years old Total: n = 60	Group I (n = 40): 50–100 mg zinc sulfate (equivalent to 11–22 mg elemental zinc) Group II (n = 20): placebo (cornstarch) twice daily 90 days	None	serum zinc serum leptin anthropometric measurements	Group I: 53.2 ± 8.15 µg/dL to 90.75 ± 12.2 µg/dL Group II: 55.45 ± 9.1 µg/dL to 55.35 ± 9.15 µg/dL	Decrease in leptin; Increase in BMI and body weight; Negative association between serum zinc and leptin levels	[27]
HD	Patients on HD with low serum zinc levels (<65 µg/dL) Total: n = 70	Polaprezinc group (n = 35): polaprezinc, 34 mg/day of zinc Control group (n = 35): no supplementation 12 months	Epoetin alph	ERI (erythropoietin responsiveness index); Weekly ESA dose (units)/dry weight (kg)/hemoglobin (g/dL)	Polaprezinc group: 53 ± 6 µg/dL to 80 ± 18 µg/dL Control group: 55 ± 5 µg/dL to 56 ± 10 µg/dL	Decrease in ESA dosage and ERI; No changes in Hb; No Change in serum iron or TSAT; Decrease in ferritin; Decrease in copper	[3]
HD	RCT Zn-deficient diabetic HD patients Total: n = 46	Zn supplement group (n = 21): 220 mg/day Zn sulfate capsule (containing 50 mg Zn) Control group (n = 25): placebo capsule (220 mg corn starch) 8 weeks	None	serum levels of copeptin, high-sensitive C-reactive protein (hs-CRP) glycemic control anthropometric parameters renal function	Zn supplement group: 55.9 ± 8.0 µg/dL to 90.6 ± 15.7 µg/dL Control group: 68.26 ± 6.2 µg/dL to 68.5 ± 6.5 µg/dL	Decrease in serum copeptin, hs-CRP, BUN, Cr, and FBG levels; Increase in BMI and body weight; No change in QUICKI (quantitative insulin sensitivity check index), HOMA-IR (homeostasis model assessment—insulin resistance), or serum insulin	[15]

Table 2. *Cont.*

Mode	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	Before–after trial Patients with serum Zn < 60 μg/dL Total: n = 21	Zinc acetate hydrate 50 mg 6 months	None	erythropoietin resistance index (ERI) ERI = dose (IU) of erythropoiesis-stimulating agent (ESA)/week/body weight (kg)/hemoglobin content (g/dL)	52.4 ± 7.6 μg/dL to 84.1 ± 16.3 μg/dL	Decrease in ERI and ESA dose; No change in Hb	[28]

Zn: zinc, HD: hemodialysis, PCR: protein catabolic rate, BMI: body mass index, ESA: erythropoiesis-stimulating agent, Hb: hemoglobin.

5. Selenium and Selenium Deficiency

5.1. Selenium and Selenium Deficiency

Selenium (Se) is also an important trace element for the maintenance of life. Its functions are described as follows: (1) it promotes the immune system, especially to maintain cellular immunity; (2) it inhibits cancer; (3) it is a constituent of glutathione peroxidase, a representative antioxidant enzyme, and has antioxidant effects; and (4) it is involved in the synthesis and degradation of thyroid hormones. Selenium is a mineral and a trace element but not a metal element. Selenium is a homologous element of sulfur; therefore, selenoamino acids exist in place of amino acids containing sulfur, including selenomethionine and selenocysteine. t-RNA that carries these amino acids, and selenoamino acids are incorporated into proteins, i.e., selenoproteins. In humans, 25 types of selenoproteins have been found (Table 3), major of which are the glutathione peroxidase family, thioredoxin reductase, and iodothyronine deiodinase.

Table 3. The lists of Selenoproteins.

Glutathione peroxidase (GPx)	GPx1 Gpx2 GPx3 Gpx4 Gpx6	The biochemical function of glutathione peroxidase (GPx) is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water.
Thioredoxin reductases (Txnrd)	TrxR1 TrxR2 TrxR3	Thioredoxin reductases (TrxR) are the enzymes that catalyze the reduction of thioredoxin; hence, they are a central component in the thioredoxin system. Together with thioredoxin (Trx) and NADPH, this system's most general description is as a system for reducing disulfide bonds in cells. They contribute to the antioxidant effects.
Iodothyronine deiodinase (DIO)	DIO1 DIO2 DIO3	Iodothyronine deiodinase (DIO) an important enzyme in the activation and deactivation of thyroid hormones. Thyroxine (T_4), the precursor of 3,5,3′-triiodothyronine (T_3), is transformed into T_3 by deiodinase activity.
Selenoprotein	SelH SelI SelK SelM Sel15 SelN SelO SelP SelR SelS SelT SelV SelW	Selenoproteins (Sels) are composed of 13 proteins that contain selenium in the molecule. Selenoprotein P is the most common selenoprotein found in the plasma. It is unusual because in humans, it contains 10 s residues.

The American Society for Parenteral and Enteral Nutrition has defined symptoms of selenium deficiency as cardiomyopathy, myalgia, myositis, hemolysis, cellular immune disorders, nail and hair abnormalities, large cell changes in red blood cells, and anemia. Nail and skin abnormalities are also observed due to the involvement of selenium in DNA synthesis. In 2017, diagnostic criteria for selenium deficiency were developed (Figure 3) [29]. The presence of any one clinical symptom can be recognized by changes such as whitening, deformity, dermatitis, and alopecia in the nails and skin; cardiomyopathy and abnormalities of the conduction system in myocardial disorders; muscle weakness and myalgia in the lower extremities in muscular disorders; and macrocytic anemia in blood data. Laboratory findings may include abnormal thyroid hormones, abnormal muscle enzymes, and liver abnormalities. Electrocardiogram changes may also be present. If one or more of these symptoms and laboratory findings is present, other diseases can be ruled out, the serum

selenium level is low, and the patient is considered suspicious and should be considered for supplementation. If the symptoms improve with supplementation, the case is confirmed. The standard serum concentration is 10 μg/dL or 100 pg/mL in adults.

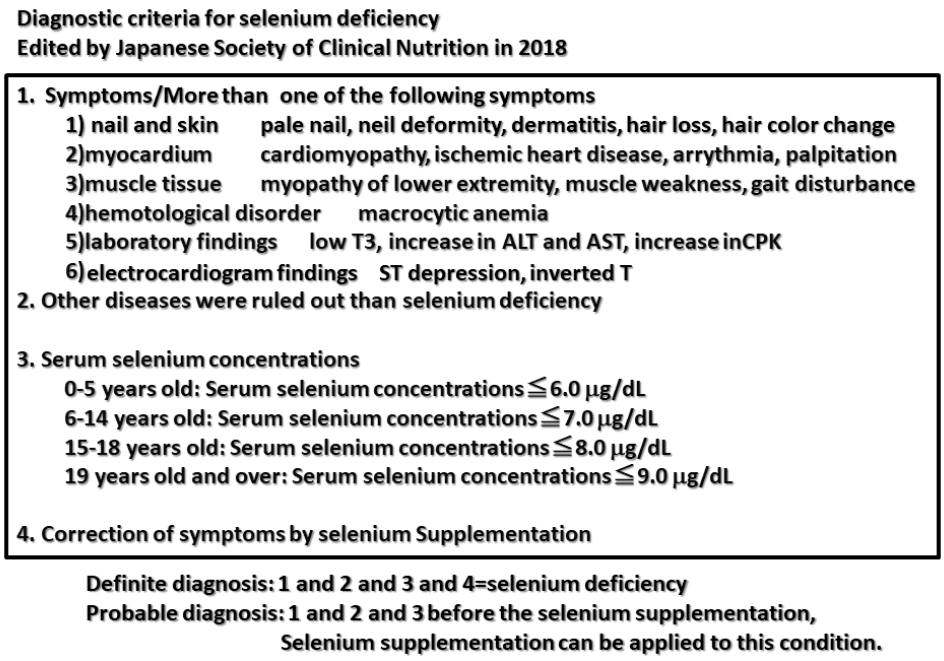

Figure 3. Diagnostic criteria for selenium deficiency. The criteria were edited by the Japanese Society of Clinical Nutrition in 2018 [29]. Reprinted with permission from [29], in 2018 from Hiroko Kodama.

5.2. Selenium Deficiency in Dialysis Patients

Dialysis patients are known to be a risk population for selenium deficiency. Possible causes include decreased selenium intake due to decreased dietary protein intake, decreased selenium-binding proteins, increased selenium requirements, increased urinary excretion, loss from dialyzer membranes, and altered distribution of selenium in the body. There are few case reports of selenium deficiency up to supplementation in dialysis patients. Myocardial symptoms were the main symptoms, with concentrations of less than 2.5 μg/dL and 8 μg/dL, both of which recovered after 3–4 months of supplementation [30,31]. In contrast, a very detailed cohort study of patients on dialysis as a whole was reported in Iwate Prefecture in Japan in 2011 [32]. Blood levels were measured in a multicenter cohort of dialysis patients, and the overall mean was significantly lower in dialysis patients than in healthy controls, with a median value of 10.3 μg/dL. When the cohort was divided into four groups based on serum selenium levels, BMI and serum albumin levels were significantly correlated. The group with the lowest serum selenium concentration had a significantly lower survival rate than the other groups in all-cause and infectious disease mortality [33]. Recently, studies on selenium and life expectancy have been reported in other countries. A study conducted in Alberta, Canada, reported the results of routine measurements of 25 trace elements [34]. Data on 25 trace elements were collected from 1278 multicenter hemodialysis patients. This cohort was followed-up for 2 years to determine which trace elements were associated with death, cardiovascular accidents, systemic infections, and hospitalizations. In 2 years, there were 260 (20%) deaths, 285 (24%) cardiovascular accidents, 117 (10%) systemic infections, and 928 (77%) hospitalizations. When investigating the relationship between 25 trace elements, low selenium levels were significantly associated with death and total hospitalization. Whereas high levels of copper and cadmium were associated with death, low levels of zinc and magnesium and high levels of lead, arsenic, and mercury were not associated with death or hospitalization, contrary to our expectations. In dialysis retrospective observational cohort study conducted in Spain that included 85 patients with ESRD on three modalities of dialysis, selenium was considered to be closely

related to death, with a plasma selenium test performed 5–6 years before the study. Patients with low selenium showed an increased risk of all-cause mortality (hazard ratio, 2.952) compared with patients with normal or high selenium [35]. Although these data were observational and other important factors may contribute to the mortality of dialysis patients, these reports from three independent cohorts imply that selenium has some roles in the prognosis of dialysis patients.

In relation to mortality, special attention should be paid in terms of the causal relationship between infection and selenium status. As previously stated, in a hemodialysis cohort study conducted in Iwate prefecture in Japan, complication with infectious disease affected the selenium status, and supplementation of this element was found to help to ameliorate the condition in infectious disease. More recently, the relationship between COVID-19 infection and selenium deficiency was investigated [36]. Chinese cohort surveillance revealed an association between the reported cure rates for COVID-19 and selenium status in one city. Antiviral effects of selenium have been reported previously, and multiple cellular and viral mechanisms involving selenium and selenoproteins may influence viral pathogenicity, including virally encoded selenium-dependent glutathione peroxidases. Furthermore, a meta-analysis consisting of a total of 13 RCTs comparing selenium and placebo for patients with sepsis were reported [37]. The analyses could not detect the association of selenium treatment with a decreased mortality at different time courses. Selenium supplementation did not show a favorable effect on the incidence of renal failure, secondary infection, or duration of mechanical ventilation. However, the study found that selenium therapy was a benefit for sepsis patients, with reduced duration of vasopressor therapy, time in the intensive care unit and hospital, and incidence of ventilator-associated pneumonia.

Cardiovascular complications are also important causes of death in dialysis patients. The relationship between selenium and cardiovascular diseases has been explored since the famous selenium-deficient disease in which Kashan disease was presented with symptoms of dilated cardiomyopathy. A randomized control trial was performed in France in 1989 in which the effects of oral treatment with 500 μg selenium for 3 months and 200 μg for the next 2 months were tested in terms of cardiac function. As compared with the placebo control, the IVS (interventricular septum) in an echocardiogram decreased, although the cardiac function did not change [38]. In another study, a correlation between decreased serum selenium levels and coronary flow reserve was examined as an indicator of endothelial dysfunction and atherosclerosis in HD patients. Serum selenium levels and coronary flow reserve values were significantly lower in hemodialysis patients compared with controls. There was a significant positive correlation between coronary flow reserve and serum levels of selenium. A linear regression analysis showed that serum levels of selenium were independently and positively correlated with coronary flow reserve [39].

The association between selenium and anemia has been shown in hemodialysis patients. A cross-sectional study was performed, and serum selenium levels were determined in 173 hemodialysis patients. The association of serum selenium with the responsiveness to erythropoiesis-stimulating agents, as defined by the ESA resistance index, was analyzed. First, the study showed that 50% of the subjects had lower selenium levels than the population-based reference values. The authors also found that serum selenium levels were significantly and inversely correlated with the erythropoiesis resistance index (ERI) but not transferrin saturation (TSAT) or ferritin levels. Moreover, an independent association between selenium levels and ESA hyporesponsiveness was detected in multiple regression analyses. When patients were divided according to selenium levels and iron status, both low serum selenium (<10.5 μg/dL) and iron deficiency significantly affected the response to ESA. Finally, the association of low serum selenium with ESA hyporesponsiveness persisted after adjustment of confounding variables [40].

Finally, the association between blood trace element levels and sleep quality in patients on maintenance hemodialysis was reported. This cross-sectional and single-center study performed in 2019 examined sleep quality in 121 enrolled HD patients with the use of the

Pittsburgh Sleep Quality Index, which revealed an association between low blood selenium levels and the occurrence of severe sleep disturbances. [41].

5.3. Treatment of Selenium Deficiency in Dialysis Patients

Selenium supplementation in dialysis patients has been attempted for a long time. A lists of these trials is presented in Table 4 [38,42–51]. The treatment protocol has not been well-determined and varies, including intravenous treatment with 400 mg of sodium selenite. In Japan, sodium selenite solution containing of 100 µg of selenium (Fujimoto Co., Ltd., Osaka, Japan) is administered by daily infusion for the treatment selenium deficiency. In almost all studies, serum selenium concentration and glutathione peroxidase (GPx) activity in serum or red blood cells increased, and several biological markers were improved, including oxidative stress. In a more recent studies, selenium tablets or capsules are frequently used in trials. In 2013 one randomized, double-blind, placebo-controlled trial was conducted using selenium (200 µg) or a placebo capsule daily for 12 weeks [47]. The authors observed that the nutritional condition index, subjective global assessment (SGA) score, the systemic inflammation and nutrition condition score, and the malnutrition inflammation score (MIS) decreased significantly in the selenium group compared to the placebo group. Moreover, serum levels of malondialdehyde (MDA), an oxidative stress marker, decreased significantly in the selenium group compared with increasing levels in the placebo group. Selenium supplementation also hindered an increase in IL-6 levels compared with the placebo group. It can be concluded that selenium may be an effective complementary supplement for reducing the severity of malnutrition in HD patients by alleviating oxidative stress and inflammation.

Table 4. Clinical trials of selenium.

Subject	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	Se group: n = 39 Control group: n = 15	500 µg oral administration for 3 months and 200 µg for the next 2 months	None	Serum GPx, GPx in RBC, and muscle volume IVS in echocardiogram	3.83 µg/dL to 9.0–8.0 µg/dL	Increase in serum GPx and GPx in RBC; Increase in muscle volume; Decrease in IVS	[38]
HD	Se group: n = 6	50 µg intravenous administration for 5 weeks and 100 µg for the next 15 weeks	Intravenous Zn gluconate for 20 weeks	Serum GPx, GPx in RBC, serum TBARs, and serum Zn	0.45 µmol/L to 0.89 µmol/L	Increase in serum GPx and GPx in RBC; Decrease in serum TBARS; No change in serum Zn	[42]
HD	Se group: n = 10 Placebo group: n = 5	500 µg oral administration for 3 months and 200 µg for the next 3 months	None	Serum Se fT3 and TSH	Se group: 7.68 µg/dL Placebo group: 5.30 µg/L	Increase in serum Se; Increase in fT3; Decrease in TSH	[43]
HD	Se group: n = 12	400 mg Intravenous sodium selenite after HD for 8 weeks	None	Serum Se and α-tocopherol, Se and α-tocopherol in RBC Serum ascorbic acid, serum retinol, serum glutathione, GPx, SOD activity in RBC, and serum MDA	Serum Se: increased to 8.37 µg/dL 4 weeks after the treatment Se in RBC: increased to 15.9 µg/dL 4 weeks after the treatment	GPx activity: increase in serum levels and no change in RBC; Decrease in MDA; No change in CAT or SOD activity	[44]

Table 4. *Cont.*

Subject	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	Total: n = 793 Divided into 3 groups Three-affiliation prospective, randomized, single-blind study	Oral selenite Se 28 µg, Oral selenate Se 28 µg Control oral Se 7 µg 14 days	Energy intake of 35 kcal/kg/day	Serum GPx, GPx in RBC, and Se in RBC	Selenite group: 1.4 µmol/L Selenate group: 1.5 µmol/L Control group: 1.2 µmol/L	No differences in serum GPx, GPx in RBC, or Se in RBC	[45]
HD	4 groups n = 15 in each group	Erythropoietin (EPO) 2000 × 3/week Se-rich yeast 300 µg × 3/week	1. Placebo 2. EPO 3. Se-rich yeast 4. EPO + Se-rich yeast	Serum GPx and GPx activity in RBC	Increased to 120, 110, and 150 ng/mL in Se concentration in serum, blood, and RBC. Se concentration in serum and blood plateaued. Se in RBC increased to 200–250 ng/mL.	Increase in GPx activity in RBC in groups 3 and 4; No change in serum GPx	[46]
HD	Total: n = 80 Se group: n = 29 Placebo group: n = 36 Randomized, double-blind, placebo-controlled study	200 µg/day oral administration for 12 weeks	None	Primary; SGA Secondary: MDA, IL-6, high-sensitivity CRP, homocysteine, transferrin, ferritin, MIS, and Hb	Not measured	Decrease in SGA and MIS; Decrease in MDA; No change in IL-6, high-sensitivity CRP, homocysteine, transferrin, ferritin, or Hb	[47]
HD	Total: n = 150 Three groups n = 50 in each group Randomized, double-blind, active-control study	Se capsule 1. standard supplementation (SS) (vitamins) 2. Low supplementation (LS) SS + vitamin E 250 IU + Zn 25 mg + Se 5 µg 3. Moderate supplementation (MS) SS + vitamin E 250 IU +Zn 50 mg + Se 75 µg	Standard supplementation; biotin 300 µg, folic acid 1 mg, nicotinamide 20 mg, thiamine 1.5 mg Cyanocobalamin 6 µg, riboflavin 1.7 mg, pyrydoxine 10 mg, ascorbic acid 100 mg	Primary: incidence of low Se and low Zn after 90 days Secondary: incidence of low Se and low Zn after 180 days Low Zn: Zn < 815 µg/L Low Se: Se < 121 µg/L	Day 90: SS: Se, 13.1 µg/dL LS: Se, 14.0 µg/dL MS: Se, 14.6 µg/dL Day 180: SS: Se, 13.5 µg/dL LS: Se, 13.5 µg/dL MS: Se, 13.0 µg/dL	Primary and secondary outcomes: No difference among three groups; No difference in sodium sensitivity or intradialytic body weight gain	[48]
HD	Total: n = 68 Se and NAC (N-acetylcysteine) treatment 4 groups each n = 17 12 weeks	Group A:placebo Group B: NAC 600 µg/day Group C: Se 200 µg/day Group D: Se 200 µg/day+ NAC 600 µg/day	NAC N-acetylcysteine	Free tri-iodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and reverse T3 (rT3)	Not measured	Decrease in rT3 levels in groups B, C, and D; No change in FT3, FT4, and TSH between the groups; Good effects on nonthyroidal illness syndrome (NTIS)	[49]

Table 4. *Cont.*

Subject	Number	Treatment Route	Combination	Evaluation	Se Concentration	Outcome	Ref.
HD	53 diabetic HD patients Randomized, double-blind, placebo-controlled trial	Selenium group (n = 26): 200 µg selenium per day Placebo group (n = 27) for 24 weeks	None	Carotid intima-media thickness, FPG, insulin, HOMA-IR, QUICKI, triglycerides, VLDL-C, total-C, LDL-C, HDL-C, CRP, total nitrites, TAC, GSH (total glutathione), and MDA	Not measured	Decrease in serum insulin levels, insulin resistance, total cholesterol, LDL cholesterol, and CRP; Increase in insulin sensitivity, HDL cholesterol, and GSH; No change in carotid intima-media thickness	[50]
HD	Total: n = 78 Intervention: n = 40 Placebo: n = 38 Double-blind clinical trial	400 µg Oral selenium vs. placebo tablets three times after each hemodialysis session for 3 months	None	Blood Se levels, serum triglyceride, total cholesterol, weight, and physical activities (five times sit to stand test)	Intervention: 40 to 65 µg/L Placebo: 45 to 42 µg/L	Increase in Se concentration and physical activity in intervention group; No change in triglycerides, total cholesterol, or body weight in either group	[51]

HD, hemodialysis; Se, selenium; RBC, red blood cell; Zn, zinc; IVS, interventricular septum; TBARS, thiobarbituric acid reactive substances; GPx, glutathione peroxidase; T3, tri-iodothyronine; SOD, superoxide dismutase; TAC, total antioxidant capacity; GSH, total glutathione; MDA, malondialdehyde; MIS, malnutrition–inflammation score; Hb, hemoglobin; SGA, subjective global assessment.

5.4. Several Controversies about Selenium Supplementation

5.4.1. Optimal Serum Concentration of Selenium

A therapeutic threshold should be established with respect to the effectiveness of serum selenium concentrations. A U-shaped phenomenon is observed for the optimal selenium concentration. Thus, selenium should not be supplemented at overdosage levels. A previous study, selenium therapy had no effects on subjects with normal selenium concentration, and only half of the subjects exhibited an increase in GPx activity [52]. On the other hand, anticancer effects were not evident in patients with very low concentrations of selenium.

5.4.2. The Tissue Distribution of Selenium

As selenium functions are incorporated in the selenoprotein enzyme, the actual physiological effects may not be evaluated by the serum concentration. To overcome this problem, the activity of GP_X in blood cells can be utilized as an alternative for the assessment of systemic selenium condition. In this regard, the normal range of serum concentration should be carefully considered.

5.4.3. Gene Polymorphism of Selenoprotein

Some SNPs or mutation on selenoproteins have been reported so far, which reduce the therapeutic effects of supplementation treatment. In these patients, supplementation is of little clinical relevance.

5.4.4. The Unique Bioavailability of Selenium

The unique characteristics of selenium bioavailability make its assessment complicated. Selenium is incorporated in selenoproteins and mobilized by a specific genetic code. In this regard, the adequate evaluation of selenium function is complex.

As selenium deficiency has some significance in the QOL and mortality of patients in end-stage renal disease, an appropriate method for assessment of selenium condition including measurement of serum concentration and cellular activity of GPx should be

developed in the future. Considering its role of survival effects, supplementation should be limited to severely compromised patients, including sepsis, SIRS, severe heart failure, or end-stage kidney disease patients. Moreover, the supplementation regimen should be carefully determined because overdose treatment has either no effects or adverse effects. Selenium is an essential and vital element that contributes to mortality, and its supplementation can open a novel path to nutrition support therapy. As selenium plays a pivotal role in the cardiovascular system and defense against infectious disease, clinical trials targeted at the patients with acute heart failure, septic shock, or acute kidney injury are optimal to confirm the efficacy of selenium intervention.

6. Copper

Plasma Copper (Cu) levels can be of clinical relevance in relation to Zn deficiency. In HD patients, as described above, the plasma Zn concentration decreases, and improper Zn supplementation can lead to Cu deficiency, since Zn antagonizes the uptake of divalent cations, including iron (Fe) and Cu, in erythrocyte precursors. Cu is required for Fe transfer from cells to blood, ensuring dietary Fe absorption and systemic Fe distribution [53]. Cu/Zn superoxide dismutase (Cu/Zn-SOD), an antioxidant enzyme, is decreased in Cu-deficient subjects, which may accelerate oxidation reactions and shorten the life span of erythrocytes. In these mechanisms, Cu deficiency may lead to refractory anemia in HD patients, and its correction can improve erythropoietin non-responsive anemia in HD patients [54].

On the other hand, elevated levels of serum Cu have been reported to trigger oxidative stress and activate inflammation [55]. The disruption of Cu and Zn homeostasis increases the risk of adverse outcomes. Significant negative associations between the Cu/Zn ratio and peripheral T-lymphocyte subsets (CD3 and CD4) and B-lymphocytes CD19 exist in CAPD patients, suggesting that variations in the Cu/Zn ratio can indicate oxidative stress and inflammation status in CAPD patients [56]. Zn supplementation significantly increases plasma Zn concentration, decreases Cu concentration and the Cu/Zn ratio, and decreases C-reactive protein and proinflammatory cytokine concentrations in HD patients [25].

7. Chromium

Chromium (Cr) levels in dialysis patients are regarded to be of clinical importance. One cohort study revealed higher concentrations of Cr than normal control in patients with ESKD [34]. In particular, in PD patients, Cr toxicity has been of clinical interest, and the consideration and measurement of dialysate fluid of PD may be necessary in the future [57]. The role of Cr can be either beneficial or harmful, depending on the ionic form. It is well established that Cr (VI) ions can easily enter cells and are associated with oxidative stress due to the reduction to Cr (III) in vivo [58]. In contrast, the more commonly found Cr (III) ion is much less dangerous or may actually be beneficial [58]. Serum Cr concentration is negatively associated with malnutrition in HD patients [59]. A prospective observational study is required to determine its toxicity to PD or HD patients.

8. Manganese

Serum manganese (Mn) levels are reported to be low in hemodialysis patients [60]. The main mechanisms for this deficiency include that Mn absorption is possibly decreased in the iron deficiency state [61], providing an additional rationale for Mn deficiency in HD patients, who are often iron deficient. Another mechanism deduced that dietary sources of Mn include meat, fish, nuts, and dried fruit [62], and the intake of these materials is often restricted in hemodialysis patients. However, a recent study reported that in Canada, there was no evidence that low Mn concentrations exist in hemodialysis patients [63]. Similar results were reported in a Spanish cohort [64]. Several previous reports have revealed the clinical consequences of Mn deficiency in hemodialysis patients. A low blood Mn level was independently associated with lower hemoglobin levels and anemia in patients undergoing hemodialysis [65]. This association was also observed in data and sample information of 110 hemodialysis patients downloaded from the UC San Diego

Metabolomics Workbench public repository. Patients with scarce response to erythropoiesis-stimulating agents (ESAs) were shown to be characterized by reduced Mn-to-nickel and Mn-to-antimony (Sb) ratios, which showed that Mn plays a role in the mechanisms underlying the human response to ESAs [66]. Low intake of Mn has also been reported to be related to malnutrition and systemic inflammation [67]. However, data on Mn deficiency in hemodialysis patients are still lacking, without any Mn supplementtation study, and whether its deficiency contributes to ill health in hemodialysis patients remains unknown, with no strong argument in favor of Mn supplementation.

9. Lead

Lead (Pb) is a heavy metal that is widespread and easy to extract and work with. Because of these characteristics, it has been used for thousands of years, and Pb toxicity has been extensively documented. Pb toxicity was previously reported in hemodialysis patients. An 18-month cross-sectional and prospective study included 927 patients on maintenance hemodialysis and revealed that a high blood Pb level is associated with increased risk for all-cause, cardiovascular-cause, and infection-cause 18-month mortality [68]. Similarly, blood Pb concentrations were associated with residual renal function and hyperparathyroidism and were related to an increased hazard ratio for all-cause 18-month mortality in peritoneal dialysis patients [69]. More recent cohort studies conducted in Canada and Spain also reported that excessive Pb concentrations were common [63,64], but the improvement in environmental condition reduced the lead intoxication in dialysis patients, and a higher concentration of Pb was not associated with higher risk of clinical outcomes such as mortality and hospitalization [34]. In general subjects, Pb accumulation affects hematopoiesis and bone formation, as well as the nervous and cardiovascular systems. Pb toxicity may present nonspecific symptoms, including colicky abdominal pain, nausea, constipation, arthralgias and myalgias, headaches and inability to concentrate, and peripheral neuropathy, especially affecting the wrist and finger extensors [70,71]. Similarly, in hemodialysis patients, several studies have delineated the clinical significance of Pb toxicity. Blood Pb levels were positively associated with carpal tunnel syndrome in patients on maintenance hemodialysis [72]. A nationwide analysis linking drinking water supply records to patient data showed that in hemodialysis patients, even low levels of Pb that were commonly encountered in community water systems throughout the United States were associated with lower hemoglobin levels and higher ESA use [73]. These data endorsed the further investigation of Pb toxicity among dialysis patients. Pb tends to be accumulated in bone, and Pb toxicity is associated with bone remodeling. Secondary hyperparathyroidism in dialysis patients can result in increased release of Pb from bone stores. Under this machanism, blood Pb concentration was shown to be effectively suppressed by calcitriol therapy [74].

10. Arsenic

Arsenic (As) is a metalloid element that is naturally present in the Earth. In human beings, As accumulates in multiple tissues, including the peripheral nervous system, skin, gastrointestinal system, bone marrow, and kidneys, and is predominantly cleared from urines [75]. Chronic As poisoning predominantly affects the skin and nervous system. Symmetrical polyneuropathy and cognitive changes are common neurologic sequelae [76,77]. Underweight or malnourished humans, especially those lacking selenium, might also be at increased risk [76], suggesting that hemodialysis patients may be at higher-than-average risk of toxicity. Several previous studies have reported increased serum concentrations of As in dialysis patients [63,64]. However, scace data of clinical significance have been reported on increased As concentration in dialysis patients. One recent study reported that high serum As was associated with cardiovascular risk factors in patients undergoing continuous ambulatory peritoneal dialysis [78]. However, there is an argument that As and its compounds occur in both organic and inorganic forms. Inorganic As compounds are highly toxic, while organic As from food is considered nontoxic. Because only total As concentrations are measured in plasma samples of the hemodialysis patients, it is difficult

to determine whether the excessive plasma As concentrations could have adverse health effects on these patients.

11. Other Trace Elements

Previous reports have measured the serum or tissue concentrations of other trace elements than were described above. In a Canadian cohort, the concentrations of several trace elements in hemodialysis patients were measured and evaluated based on the 5th and 95th percentile plasma concentrations from healthy reference populations. In terms of other trace elements, excessive plasma concentrations of cobalt, vanadium, cadmium, barium, antimony, nickel, and molybdenum were common, as were low platinum, tungsten, and beryllium concentrations [63]. Using this cohort, the clinical significances were analyzed by prospective study for 2 years of followup. Higher concentrations of mercury were not independently associated with higher risk of clinical outcomes including mortality or hospitalization. Cadmium levels in the highest decile were associated with higher risk of death [34]. In a Spanish cohort, it was reported that hemodialysis patients showed significantly higher concentrations of nickel as compared with normal controls [64]. Prior to these recent surveillance studies, a systemic review and metanalysis of 128 eligible studies was reported, and levels of cadmium and vanadium were higher [60]. Tissue concentrations of these trace elemtns were also measured to evaluate trace element deficiency or accumulation. In scalp hair of hemodialysis patients, the concentrations of beryllium, molybdenum, iodine, vanadium, and cobalt were significantly higher than those in healthy subjects, while mercury, germanium, and bromine levels were significantly lower than those in the former group. No significant differences were observed for lithium, aluminum, cadmium, boron, or nickel [79]. Significant bone accumulation of aluminium and vanadium occurred in the hemodialyzed azotemic individuals [80].

The abnormalities of several trace elements were investigated in a specific function. High cadmium levels might play a role in coronary artery calcification development in hemodialysis patients [81]. The relationship between serum nickel and homocysteine concentration was reported in hemodialysis patients, and nickel might also be involved in the regulation of the methionine-folate cycle in humans [82]. Finally, a multicenter study indicated that patients from particular dialysis centers are at an increased risk for strontium accumulation [83], and an association between osteomalacia and increased bone strontium concentrations in dialysis patients was reported [84]. However, all these clinical data were obtained in a cross-sectional or observational study, and a cause-and-effect relationship has not been demonstrated. Moreover, the methods of measurement were not the same between past and the recent studies, and the soil, drinking water, and dialysate water contents of trace elements varied among areas or countries. Confirmation of these clinical data awaits further investigation.

12. Conclusions

The major causes of death in dialysis patients are heart failure and infections, which may be closely related to poor nutrition. Although not specific to any one nutrient, trace element deficiency or toxicity is also a factor that cannot be ignored. For example, it has been reported that selenium deficiency is associated with infection and cardiac dysfunction and that its deficiency may affect the life expectancy of hemodialysis patients. However, in most trace elements other than Zn or Se, only association or observation studies have been reported, and there has been no consensus with respect to supplementation of these elements. Additional investigations are necessary to confirm the efficacy of intervention in the future.

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