Micronutrients and Cardiorenal Disease: Insights into Novel Assessments and Treatment

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Key Words

Cardiorenal syndrome • Chronic kidney disease • Acute kidney injury • Cardiovascular disease • Nutrition • Micronutrient

Abstract

Chronic kidney disease (CKD) is a recognized risk multiplier for development of cardiovascular disease (CVD), with CVD events representing the leading cause of morbidity and mortality in patients with CKD. The nature of CKD as a risk state relates both to the nature of CKD and the antecedent development of CVD. In addition, patients with CKD have increased rates of multiple conventional cardiac risk factors. The essence of the relationship appears to be bidirectional, and therapy directed at improving natural history of chronic disease on one system generally improves prognosis in the other. Hence the term 'cardiorenal syndrome' (CRS) is used to describe the complex interrelationships between the two organ systems. While focus on therapeutic targets has been dominated by interest in neurohormonal mechanisms, little attention has been given to micronutrients and their potential effects in CRS. As renal function declines, cellular metabolism changes profoundly, and when artificial means of solute removal are initiated by peritoneal dialysis or hemo-

dialysis, there are considerable shifts of many micronutrients that may affect cardiovascular health predominantly through the mechanism of increasing labile iron-dependent oxidative stress. Release of labile iron at the tissue level appears to be most important in acute CRS, whereas phosphate and sodium retention play more of a role in chronic CRS. Attention will be given to selected micronutrients which may call for novel assessments and intervention for optimal cardiorenal outcomes.

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Introduction

Both cardiac and renal diseases commonly present in the same patient and have been associated with increased cost of care, complications, and mortality [1, 2]. Cardiorenal syndromes (CRS) describing the dynamic interrelationship between heart and the kidney malfunction have been defined in a recent consensus process by the Acute Dialysis Quality Initiative [3]. This has generated five distinct syndromes upon which the epidemiology of CRS has been described. There have been no publications specifically addressing the issue of micronutrient assessment and cardiorenal implications.

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Generation of reactive oxygen species with dependence on labile iron in reactions 4 and 5
Reaction 1 $\rightarrow \text{O}_2 + \text{e}^- \rightarrow \cdot\text{O}_2^-$ Reaction 2 $\rightarrow \cdot\text{O}_2^- + \cdot\text{O}_2^- + 2\text{H}^+ \rightarrow \text{O}_2 + \text{H}_2\text{O}_2$ Reaction 3 $\rightarrow \text{H}_2\text{O}_2 + \cdot\text{O}_2^- \rightarrow \text{OH}^- + \text{OH}^\bullet + \text{O}_2$ Reaction 4 $\rightarrow \text{Fe}^{3+} + \cdot\text{O}_2^- \rightarrow \text{Fe}^{2+} + \text{O}_2$ Reaction 5 $\rightarrow \text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^\bullet$ Reaction 6 $\rightarrow \text{H}_2\text{O}_2 + \text{Cl}^- + \text{H}^+ \leftrightarrow \text{H}_2\text{O} + \text{HOCl}$
Cl ⁻ = Chloride; e ⁻ = electron donor; Fe ³⁺ = ferric iron; Fe ²⁺ = ferrous iron; H ₂ O ₂ = hydrogen peroxide; OH ⁻ = hydroxyl; OH ⁻ = hydroxide; O ₂ = oxygen; $\cdot\text{O}_2^-$ = superoxide anion.

Fig. 1. Chemical equations for the generation of oxygen free radicals and oxidative stress.

Micronutrients and CRS

The term CRS suggests the presence of multiple syndromes with subtypes denoted by the principal organ dysfunction (cardiac versus renal or simultaneous) as well as the relative acuity of the condition. Both organs must have or develop pathological abnormalities to fulfill the criteria for definition. The umbrella term ‘*cardiorenal syndromes*’ was defined as ‘disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other’. Five subcategories of the CRS are given below. Proposed pathophysiological mechanisms are described for each syndrome.

Labile Iron-Dependent Oxidative Stress as a Common Mechanism of Acute and Chronic Organ Injury

The process of oxidative stress resulting in cell dysfunction, accelerated apoptosis, and death is reliant on the cytosolic and extracellular presence of labile or catalytic iron. There are several steps in generation of reactive oxygen species (ROS) as shown in figure 1. Oxygen may be reduced to form superoxide anion, which can then either dismutate or go through another reduction reaction by superoxide dismutase to form hydrogen peroxide which itself can then be reduced through several pathways. In total, the net Fritz-Haber reaction is slow and in the presence of reduced transition metals such as ferric iron, a Haber-Weiss reaction results in the formation of the highly damaging hydroxyl radical from the superoxide anion. In the presence of ferrous iron, a Fenton type reaction converts hydrogen peroxide to the highly dam-

aging hydroxyl radical. Further reduction of hydroxyl radical finally ends in the formation of water. It has been theorized that a common element to all forms of oxidative stress to the heart and kidneys involves the availability of unbound iron (not bound to transferrin, ferritin, or otherwise measurable by standard iron studies) [4]. The body has an intricate management system for iron metabolism keeping it bound in transport proteins, heme, and cellular organelles for normal functioning [5, 6]. If small amounts of iron are released from adjacent injured cells and not bound, this poorly liganded (labile or catalytic) iron in either the ferric or ferrous states, can facilitate the rapid generation of oxygen free radicals and the propagation of oxidative stress and injury across regions of vascular tissue [7]. Thus, it is possible that the fundamental pathophysiological basis for CRS is the loss of control over normal iron management after insults to either the heart or the kidneys in the form of hypoxia, chemotoxicity, or inflammation. It has been shown that patients with end-stage renal disease (ESRD) not receiving iron infusions have higher levels of poorly liganded iron [8]. On top of this baseline, many patients with chronic kidney disease (CKD) and ESRD receive iron infusions for the treatment of anemia in the form of iron dextran; sucrose, polymaltose, and saccharate have been linked to transient increases in measurable catalytic iron in the bloodstream which persist in ~20% of patients with ESRD [9–13]. In one study of 20 healthy volunteers, this transient rise in poorly liganded iron led to increased measures of oxidative stress and endothelial dysfunction [14]. Of all the iron preparations, ferric carboxymaltose appears to have the least catalytic iron measurable after infusion [15]. The long-term cardiorenal risks of iron infusions and transient exposures to systemic labile iron and oxidative injury are unknown.

Measurement of Catalytic Iron

Iron is the most common metal element in the human body, and there are elaborate transport and management systems for its use in a variety of critical cellular systems including oxygen transport and cellular respiration. It has been known that poorly liganded iron is the critical basis for the generation of the hydroxyl radical, which is the most destructive of all ROS. Using the bleomycin detectable assay, Lele et al. [16] have recently demonstrated the release of catalytic iron into the blood in patients with acute coronary syndromes (ACS). In this study, the appearance of catalytic iron preceded the rise in serum troponin and had an area under the receiver operating characteristic curve for the detection of acute myocardial in-

fraction over 0.90. Labile iron is also believed to play an essential role in the oxidative organ damage of acute kidney injury (AKI) as discussed above [17]. It is believed that local cellular and tissue availability of catalytic iron determines the degree and severity of organ injury in the setting of most hypoxic and other toxic insults [18]. Thus, catalytic iron may serve as both a diagnostic and therapeutic target by using iron chelators in the future for CRS [19]. With the understanding that labile-dependent oxidative stress is probably a mechanism common to all five forms of CRS, within each subtype, there are additional micronutrient issues as discussed below.

Specific Micronutrient Targets for CRS

Five proposed clinical scenarios where combined heart and kidney injury and dysfunction are recognized are drawn in figure 2. Highlighted in red is the concept that labile iron-dependent oxidative stress is a component of the acute CRS, while retention of phosphate and sodium play greater roles in chronic CRS.

Acute CRS (Type 1): Acute Decompensation of Cardiac Function Leading to AKI

This is a syndrome of worsening renal function that frequently complicates acute decompensated heart failure (ADHF) and ACS. The other major clinical scenario where CRS type 1 develops is in the setting of urgent or elective coronary revascularization for acute or chronic coronary disease. Acute contrast-induced and cardiopulmonary bypass surgery-associated AKI occurs in 15 and 30% of patients, respectively [20, 21]. Importantly, iodinated contrast which causes renal vasoconstriction and direct cellular toxicity to renal tubular cells is an important preexisting factor in the few days before cardiac surgery. Cardiac surgery exposes the kidneys to hypothermic, pulseless reduced perfusion for 30–90 min, and thus represents a superimposed ischemic injury in the setting of a proinflammatory state [22]. It is possible that the extracorporeal circuit used in cardiopulmonary bypass surgery activates systemic factors that further induce AKI; however, attempts to limit this exposure have not resulted in statistically reduced rates of AKI [23]. Thus, these two scenarios are tightly linked since almost every cardiac surgery patient operated upon in the urgent setting undergoes coronary angiography in the hours to days before surgery [24]. As with ADHF, CRS type 1 in acute and chronic coronary disease has a confounded relationship with outcomes. In those with complications, CRS type 1 appears to be independently associated with a three- to fourfold increase in mortality despite the availability of

dialysis in the hospital [25, 26]. In all forms of CRS type 1, there is a risk of advancing to higher stages of CKD and ultimately the need for chronic renal replacement strategies [27]. The major micronutrient approaches for CRS type 1 in the setting of planned contrast exposure include the use of ascorbic acid (found in citrus fruit) and N-acetylcysteine (found in high protein foods such as meat and eggs). Both of these approaches work to reduce oxidative stress by attempting to rejuvenate antioxidant systems. They do not work to attenuate the generation of labile iron-dependent oxygen free radicals. Thus, both approaches have had inconsistent results in clinical trials (either after iodinated contrast or with cardiac surgery), and at this time do not have US Food and Drug Administration indications as prophylactic treatment [28, 29]. The most promising approach is the use of high-dose N-acetylcysteine (>600 mg of precontrast exposure) with intravenous sodium bicarbonate, which may work to slow the catalytic iron-dependent oxidative stress reactions. In a recent meta-analysis of 10 randomized trials using this approach, there was a significant reduction in the rates of contrast-induced AKI, but not ESRD or death [30].

Chronic CRS (Type 2): Chronic Abnormalities in Myocardial Function Leading to Worsened CKD

This subtype implies that chronic cardiovascular disease (CVD) can contribute to the development of CKD. Chronic abnormalities in systolic and diastolic myocardial performance can lead to alterations in neurohormonal activation, renal hemodynamics, and a variety of adverse cellular processes leading to apoptosis and renal fibrosis [31]. Approximately 30% of those with CVD meet a definition of CKD, and multiple studies have demonstrated the independent contribution of CVD to the worsening of CKD [32]. An important component of CRS type 2 epidemiology is that CKD appears to accelerate the course of atherosclerosis and result in premature CVD events including MI and stroke [33, 34]. Importantly, CKD and its metabolic milieu work to cause advanced calcific atherosclerosis through the process of CKD mineral and bone disorder characterized by phosphate retention, relative vitamin D and calcium availability, and secondary hyperparathyroidism [35]. Of these factors, phosphate retention appears to be the critical pathophysiological component stimulating the conversion of vascular smooth muscle cells to osteoblastic-like cells which, via the Pit-1 receptor, are stimulated to produce extracellular calcium hydroxyapatite crystals in the vascular smooth muscle layer of arteries [36, 37]. Despite being intuitive, there are no relationships between oral calcium

Fig. 2. Pathophysiology and definitions of the five subtypes of CRS featuring labile iron-dependent acute oxidative stress in acute CRS and retention of sodium and phosphate in chronic CRS. CRS = Cardiorenal syndromes; CVP = central venous pressure; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; DM = diabetes mellitus; HTN = hypertension; ATN = acute tubular necrosis; CHF =

congestive heart failure; LVH = left ventricular hypertrophy; EPO = erythropoietin; LPS = lipopolysaccharide; ADHF = acutely decompensated heart failure; ACS = acute coronary syndrome; ROS = reactive oxygen species; CI-AKI = contrast-induced AKI; CSA-AKI = cardiac surgery-associated AKI; RAAS = renin-angiotensin-aldosterone system.

Table 1. Comparison of non-prescription vitamin supplements for dialysis patients

Ingredient	Dialyvite® 800	Dialyvite® 800 + Zinc	Dialyvite® 800 + Zinc 15	Dialyvite® 800/Ultra D	Dialyvite® 800 + Iron	NephroVite®	Allbee + C	Renavite™ + Zinc
Folic acid	800 µg	800 µg	800 µg	800 µg	800 µg	800 µg	400 µg	800 µg
Vitamin B ₁₂ methylcobalamin or cyanocobalamin	6 µg methyl	6 µg methyl	6 µg methyl	6 µg methyl	6 µg methyl	6 µg cyano	–	6 µg cyano
Pyridoxine (B ₆)	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	5 mg	10 mg
Thiamine (B ₁)	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	15 mg	1.5 mg
Riboflavin (B ₂)	1.7 mg	1.7 mg	1.7 mg	1.7 mg	1.7 mg	1.7 mg	10.2 mg	1.7 mg
Niacinamide or niacin (B ₃)	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	50 mg	20 mg
Pantothenic acid (B ₅)	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Biotin	300 µg	300 µg	300 µg	300 µg	300 µg	300 µg	300 µg	300 µg
Vitamin C	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg	300 mg	60 mg
Vitamin E	–	–	–	30 IU	–	–	–	–
Elemental iron	–	–	–	–	29 mg	–	–	–
Zinc	–	50 mg	15 mg	15 mg	–	–	–	50 mg
Selenium	–	–	–	70 µg	–	–	–	–
Vitamin D	–	–	–	2,000 IU	–	–	–	–

Ingredients in common vitamin supplements for ESRD patients suggested for use once a day. On dialysis days, give after the dialysis session. Note, none of these products has vitamin A or D (exception: Dialyvite 800/Ultra D), calcium, or many trace minerals, which must be individualized.

intake and measured blood calcium levels or vascular calcification in the general population and those with CKD [38]. Randomized trials of limiting calcium intake in ESRD have not led to attenuation in the progression of coronary calcification [39, 40]. Thus, patients as a part of CRS type 2, more commonly have vascular calcification, less vascular compliance, and a higher degree of chronic organ injury related to blood pressure elevation and shear stress [41]. Despite these mechanisms specific to CRS, CRS type 2 remains heavily confounded by the ‘common soil’ of atherosclerosis and CKD. The cardiometabolic syndrome and neurohormonal activation affect both organ systems; thus, it is difficult to tease out the temporal sequence of pathophysiological events for most individuals which are occurring over the period of decades [42].

Acute CRS (Type 3): Acute Worsening of Renal Function Leading to Cardiac Events

The most common scenario for CRS type 3 is the development of AKI that results in volume overload, sodium retention, neurohormonal activation, and the development of clinical HF with the cardinal features of pulmonary congestion and peripheral edema. Volume overload alone has been shown to induce cardiac failure and reflect CRS type 3 most clearly in the pediatric population [43]. Thus, the micronutrient most critical to CRS type 3 is sodium. In salt-sensitive individuals, increased

intake of sodium leads to abnormal circadian changes in blood pressure, and thus greater overall vascular shear stress and damage [44]. By activating the renin-angiotensin system, sodium hastens the progression of CKD and leads to greater degrees of proteinuria independent of other dietary factors [45]. Thus, the epidemiology of this CRS subtype is not well defined for individual CVD events such as ACS, stroke, cardiac rehospitalization, arrhythmias, pump failure, and cardiac death, and we must infer from other sources of cardiovascular epidemiology [4].

Chronic CRS (Type 4): Chronic Renal Disease Leading to the Progression of CVD

Over the past several decades, there has been recognition of a graded and independent association between the severity of CKD and incident as well as prevalent CVD [2]. In a meta-analysis of 39 studies (1,371,990 participants), there was a clear relationship between the degree of renal dysfunction and the risk for all-cause mortality [46]. The unadjusted relative risk for mortality in participants with reduced kidney function was in excess of the referent group in 93% of cohorts. Fourteen of the thirty-nine studies described the risk for mortality from reduced kidney function, after adjustment for other established risk factors. Although adjusted relative hazards were on average 17% lower than unadjusted relative risks,

Table 2. Components of common over-the-counter multivitamin (Centrum™)

Ingredient	Amount per serving	Unit	Percent daily value
Vitamin A (29% as beta-carotene)			70.00
Vitamin C	60	mg	100.00
Vitamin D			100.00
Vitamin E			100.00
Vitamin K	25	µg	31.00
Thiamin	1.5	mg	100.00
Riboflavin	1.7	mg	100.00
Niacin	20	mg	100.00
Vitamin B ₆	2	mg	100.00
Folic acid	400	µg	100.00
Vitamin B ₁₂	6	µg	100.00
Biotin	30	µg	10.00
Pantothenic acid	10	mg	100.00
Calcium	162	mg	16.00
Iron	18	mg	100.00
Phosphorus	109	mg	11.00
Iodine	150	µg	100.00
Magnesium	100	mg	25.00
Zinc	15	mg	100.00
Selenium	20	µg	29.00
Copper	2	mg	100.00
Manganese	2	mg	100.00
Chromium	120	µg	100.00
Molybdenum	75	µg	100.00
Chloride	72	mg	2.00
Potassium	80	mg	2.00
Boron	150	µg	
Nickel	5	µg	
Silicon	2	mg	
Tin	10	µg	
Vanadium	10	µg	
Lutein	250	µg	
Lycopene	300	µg	

Adapted from the National Library of Medicine Dietary Supplements Labels Database.

they remained significantly greater than unity in 71% of cohorts. The overall mortality was influenced greatly by excess cardiovascular deaths, which constituted over 50% of cases. Thirteen studies have been identified as specifically reporting on CRS type 4, most of which are in populations with ESRD [4]. The INTERSALT Study was a standardized, worldwide epidemiologic study of large sample size ($n = 10,079$ men and women aged 20–59 years from 32 countries) that measured 24-hour sodium excretion and blood pressure. There was a significant, positive,

independent linear relation between 24-hour sodium excretion and systolic blood pressure. With multivariate adjustment, the estimated effect of a sodium intake by 100 mmol/day (2.3 g/day) increments was higher systolic/diastolic blood pressure by approximately 3–6/0–3 mm Hg [47]. In seventeen intervention studies, sodium restriction has led to reductions in blood pressure and thus lesser need for antihypertensive medications but no improvement in CVD endpoints [48, 49]. However, a gradual worsening of renal function, in addition to excess sodium intake, has been clearly linked to cardiovascular events, most notably decompensated heart failure [50]. On the other hand, comprehensive dietary and dialytic management of sodium is one of the most promising approaches for reducing adverse events in ESRD [51].

Deficiencies of water-soluble vitamins may occur in uremic patients mainly because of restricted consumption and of loss during chronic hemo- and peritoneal dialysis. Although the daily requirement for most vitamins is not well defined in chronic renal failure, supplementation of thiamine, riboflavin, pyridoxine, pantothenic acid, niacin and ascorbic acid in the form of one multivitamin preparation without vitamin A or D as well as folic acid in dialysis patients after each dialysis session is recommended (see table 1 for common formulations) [52]. Of note, most vitamins designed for ESRD patients have fewer items and lower dose exposures than standard over-the-counter multivitamins for the general populations (see table 2). There are no published studies linking the use of multivitamins in ESRD patients to favorable CVD outcomes. Folic acid, vitamin B₆, and B₁₂ supplementation in an attempt to reduce homocysteine has been exhaustively studied in the general population, persons with heart disease, and those with ESRD. In aggregate, despite its consistent epidemiologic relationship with incident CVD, the reduction in homocysteine has not been shown to influence CVD events or mortality [53].

Secondary CRS (Type 5): Systemic Illness Leading to Simultaneous Cardiac and Renal Failure

It is recognized that a systemic insult, particularly in a younger patient with no prior heart or kidney disease, can lead to simultaneous organ dysfunction. This is almost always in the setting of critical illness such as sepsis, multiple trauma, or burns. There are limited data on the incidence and determinants of CRS (type 5) in part because confounders such as sepsis, hypotension, respiratory failure, liver failure, and other organ injury beyond the cardiac and renal systems create a difficult human

model for investigation. The nutritional demands of these extreme systemic insults call for enteral or parenteral nutrition with standard micronutrient supplementation. However, there are no published data supporting that micronutrient supplementation beyond standard electrolyte management in CRS influences either cardiac or renal outcomes.

Conclusions

There is now a consensus on the classification of CRS which has yielded a framework for a better understanding of the five subtypes of CRS [3]. Although not considered a nutritional determinant, tissue availability of labile iron and its ability to catalyze oxidative stress reactions appears to be critical in all forms of CRS as a common

pathophysiologic mechanism. For chronic CRS, phosphate intake and phosphate retention as well as sodium intake and volume overload appear to be the two most important micronutrient determinants of CRS. Randomized trials of water- and fat-soluble vitamins, to date, have not resulted in improved CVD outcomes in patients with CKD or ESRD.

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