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Zinc Deficiency and Heart Failure: A Systematic Review of the Current Literature

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Highlights

- Zinc deficiency may be a relatively common occurrence in patients with heart failure, and may be observed as a result of impaired micronutrient consumption, upregulation of the neurohormonal axis, or hyperzincuria.
- There are multiple potential pathophysiologic pathways through which zinc deficiency may contribute to the development or worsening of heart failure, including increased oxidative stress, derangements of the cardiomyocyte extracellular matrix, and loss of cardiomyocytes.
- Epidemiologic studies suggest low serum zinc levels in heart failure particularly in studies of non-ischemic cardiomyopathy.
- A small but growing body of evidence suggesting the role for zinc supplementation in the management of heart failure however further evaluation of the impact on outcomes is needed.

Zinc Deficiency and Heart Failure: A Systematic Review of the Current Literature

Short running title: Zinc and Heart failure

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Abstract

Zinc is an essential micronutrient that impacts the cardiovascular system through modulation of oxidative stress. It is unknown whether zinc levels are affected in heart failure (HF), and whether the association, if present, is causal. A systematic search for publications that report coexisting zinc deficiency in HF patients was performed to provide an overview of the pathophysiological and epidemiological aspects of this association (last search April 2019). Review of the literature suggests multiple potential pathophysiologic causes for zinc deficiency in HF as a result of impaired micronutrient consumption, hyper-inflammatory state, upregulation of the renin-angiotensin-aldosterone axis, diminished absorption, and hyperzincuria from HF medications. In a longitudinal study of patients with HF in the setting of intestinal malabsorption, there was partial cardiomyocyte and left ventricular ejection fraction recovery with intravenous selenium and zinc supplementation. Two randomized double-blind control trials evaluating micro and macro nutrient supplementation including zinc in HF patients found improvement in echocardiographic findings when compared to placebo. Two recently completed studies evaluated the role for zinc supplementation in two different HF populations: a trial of zinc supplementation in patients with non-ischemic HF, and a trial of micronutrient supplementation

(including B vitamins, vitamin D, and zinc) in veterans with systolic dysfunction; the results of which are still pending. Several pathobiological pathways to link zinc deficiency with the development and deterioration of HF are presented. Preliminary clinical data are supportive of such an association and future studies should further investigate the effects of zinc supplementation on outcomes in HF patients.

Introduction

The human heart requires energy from micro and macro nutrients both to regenerate proteins and cells, and to support cyclic contractions. (1) Heart failure (HF) is a systemic illness associated with neuro-hormonal activation leading to elevated levels of inflammatory markers and oxidative stress. Normally, micronutrients are only required in small amounts for antioxidant activities. However, in the HF state, there is increased generation of reactive oxygen and nitrogen species. As such, antioxidant enzymes – the generation of which relies on the availability of micronutrients such as zinc – are upregulated in stressed cardiac tissue, however are likely overwhelmed by the excess of the oxidant insult. This overexpression of antioxidant enzymes leads to relative myocardial zinc deficiency. (2-7) Zinc is also involved in regulation of several metalloproteases specific to HF pathophysiology, including angiotensin-converting enzyme and matrix metalloproteinases (MMPs) involved in myocardial wall structure. Decreased serum levels of zinc may lead to damage of cell membranes and a decline in cardiac function. (8,9)

In the HF state, zinc deficiency may occur as a result of diminished oral intake in individuals following a low sodium diet or due to advanced HF or age. (10) The increased systemic inflammatory state associated with cardiomyopathy may lead to further propagation of adverse remodeling in already damaged myocardium. Zinc deficiency may also play a role as a primary and possible reversible cause of cardiomyopathy. (11,12) In this systematic review, a contemporary assessment of the association between zinc deficiency and HF involving pathophysiology, epidemiology and clinical implications is described.

Methods

In compliance with PRISMA guidelines, (13) the authors performed a search of MEDLINE using PubMed interface and Scopus for studies related to zinc deficiency in association with HF as a coexisting condition, or an ensuing event, from January 1940 to April 2019. The Cochrane Database of Systematic Reviews was screened to identify possible prior systematic reviews on the topic. Clinicaltrials.gov was searched for studies of zinc supplementation in patients with CHF (Table 1). Search terms included keywords and Medical Subject Heading (MeSH) terms that referred to HF and zinc deficiency. Studies of patients with different HF phenotypes and New York Heart Association classes were included. Excluded were studies reporting the association of zinc with non-HF cardiac conditions such as atherosclerosis and ischemia/ reperfusion injury.

Results

Overall, 127 studies retrieved through PubMed search and 713 studies from Scopus were screened. No additional studies were found in search of the Cochrane database. One additional cross-sectional study was retrieved by hand-searching (Figure 1). (14) Of 168 ongoing trials on clinicaltrials.gov, two completed yet unpublished studies pertaining to zinc supplementation in HF were identified. (15,16) We provide pathophysiologic consideration from molecular and cellular, animal and human studies relevant to zinc deficiency in HF and summarize the clinical epidemiology and potential clinical impact of this association from 33 records.

Epidemiology of Zinc Deficiency in Heart Failure

Plasma zinc levels have been reported in multiple observational studies of patients with HF. Particularly in studies of idiopathic dilated cardiomyopathy, serum zinc levels have been found to be low, while results have been mixed in other etiologies of cardiomyopathy (Table 3). (12,14,17-28) In the general US population, the prevalence of zinc deficiency is between 1-4%. (29) Although the prevalence of zinc deficiency in HF patients has not been clearly reported,

average zinc levels in HF patients are significantly lower than controls in the published literature (Table 3). (12,19,22,30,31) Therefore, it is safe to assume that zinc deficiency is more prevalent in HF patients than in the general US population. Reduced serum zinc levels in HF are associated with higher New York Heart Association Class, older age, and use of ACE inhibitors and angiotensin II receptor blockers. A recently published longitudinal study of patients with zinc levels measured at discharge for decompensated HF suggests that zinc levels are $<75\text{mcg/dL}$ in 66% of patients. In patients with serum zinc levels $<62\text{mcg/dL}$ have increased cardiovascular and all-cause mortality compared to those with serum zinc levels $\geq 62\text{mcg/dL}$.(32)

Nutritional status, including zinc intake, in patients with HF has been evaluated in several cross-sectional studies (Table 2). In general, HF is associated with poor nutritional status and limited zinc intake. Even in HF patients with adequate dietary energy intake, intake of micronutrients including zinc is below daily requirements. (33) Interestingly, in a cross sectional study by Frediani et al, patients following a sodium-restricted diet (<2000 mg sodium per day) had significantly reduced micronutrient intake including zinc compared with those not following sodium restricted diet.(34)

Mechanisms of Zinc Deficiency in HF (Figure 2)

In HF of any underlying etiology, serum zinc deficiency may occur through multiple mechanisms including reduced dietary intake, reduced absorption, increased uptake in stressed tissues, and increased excretion.(35,36) Oral intake may decrease due to cardiac anorexia, accompanied by nausea and premature satiety with eating, reduced absorption due to gastrointestinal edema, (37) sodium restricted diet, or diminished oral intake in the setting of senescence. Ongoing decreased cardiac output and diminished peripheral perfusion result in a hyperadrenergic state associated with higher levels of cortisol, renin-angiotensin II-aldosterone system derivatives, and atrial natriuretic peptide (ANP). Up-regulation of these hormones has been demonstrated in both in animal and human studies to increase urinary and fecal excretion of zinc, facilitate redistribution of zinc to stressed tissues, and decrease bone zinc content due to secondary

hyperparathyroidism, all of which contribute to lower plasma zinc levels. (38-40) In animal models where plasma levels of aldosterone and sodium are raised to a level found in HF, (39,41) increased urinary excretion of zinc is associated with decreased plasma zinc, as well as decreased plasma copper/zinc superoxide dismutase activity. Aldosterone receptor activation in the epithelial cells of the kidneys leads to upregulation of a Na^+/H^+ exchanger, (42) causing acidification of the urine and metabolic alkalosis with an associated hyperzincuria. Treatment with spironolactone, an aldosterone receptor antagonist, or acetazolamide, which attenuates the acidification of the urine, helps prevent the decline in plasma levels of zinc by decreasing hyperzincuria. (39,43)

HF Medications and Their Role in Zinc Homeostasis

Medications targeted at the neuro-hormonal pathways involved in disease progression of HF that have been demonstrated to reduce serum zinc include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and thiazide diuretics. (44) Thiazide diuretics act principally at the distal convoluted tubule and significantly increase urinary excretion of zinc. On the contrary, furosemide has an unclear effect and most studies report no change in serum zinc with chronic furosemide intake. Trasobares et al. demonstrate lower serum zinc and increased urinary zinc in HF patients treated with angiotensin-converting enzyme inhibitors compared to controls. (22) Both losartan and captopril have been shown to reduce serum zinc and increase urinary zinc excretion. (45-49) Angiotensin-converting enzyme (ACE) inhibitors have a zinc binding moiety that directly binds zinc to the active site, which may lead to lower serum zinc levels. As demonstrated above, direct aldosterone blockade in animal models has the effect of increasing serum zinc levels. Further investigation should be undertaken into the role of guideline directed medical therapy for HF, including the recent addition of the use of angiotensin receptor-neprilysin inhibitors, on zinc deficiency.

Pathophysiological Implications of Zinc Deficiency (Figure 2)

Zinc Deficiency and Systemic Inflammation

Severe zinc deficiency in malnutrition has been shown to significantly reduce serum antioxidant enzyme activities that require zinc as a cofactor, leading to increased systemic inflammation and impaired immunity.(50) A zinc-deficient diet leads to decreased Type 1 T helper (Th1) related cytokines including interleukin (IL)-2 and interferon- γ and upregulated pro-inflammatory cytokines tumor necrosis factor- α and IL-1 β and IL-8. (51,52) These defenses may be further weakened in HF due to its pathophysiologic state of chronically increased oxidative stress.

Zinc's Role in Myocardial Tissue

Increased oxidative stress has been previously described in patients with HF, and correlates with disease severity.(2,3,6,53,54) In stressed cardiac tissue, increased levels of reactive oxygen and nitrogen species saturate the antioxidant defenses.(55) Mitochondrial peroxiredoxin and metalloenzymes such as superoxide dismutase rely on zinc for antioxidant reactions. As these antioxidant enzymes are saturated and a relative deficit becomes apparent due to the above mechanisms, superoxide anions react with hydrogen peroxide to form free radicals, which lead to lipid peroxidation and destruction of cell membranes(56,57) through both apoptotic and ultimately necrotic cell death pathways. Histopathologically, reduced serum zinc levels have been associated with changes suggestive of increased oxidative stress including increased autophagy and hypertrophy of myocardium, and remarkable degeneration of cardiomyocytes with extensive areas of fibrosis; changes that normalize with supplementation of zinc.(12)

With increased oxidative stress in cardiac muscle, metallothionein, a zinc binding protein is upregulated,(39) leading to increased zinc uptake and release in cardiac tissue.(58) However, the increased zinc levels in tissues occur in conjunction with increased intracellular translocation of Ca²⁺ through L type Calcium channels. Intracellular calcium acts as a pro-oxidant and causes organelle degeneration.(59,60) In particular, mitochondrial based production of reactive oxygen species exceeds the rate of detoxification of antioxidant defenses by zinc dependent

superoxide dismutase, leading to mitochondrial permeability, swelling and degeneration and ultimate cell necrosis.(61)

Furthermore, degradation of the collagenous scaffolding that provides support and maintains myocardial geometry during the cardiac cycle also relies on zinc-associated enzymes. Zinc-dependent matrix metalloproteinases (MMPs) are induced by proteolytic degradation, leading to degradation of the extracellular matrix, thinning of myocardium and progression of HF.(44,62)

Is there a Role for Zinc Supplementation?

small but growing body of evidence suggests a role of zinc supplementation in the management of HF. In a recent longitudinal study by Frustaci et al, serum and intramyocardial zinc and selenium levels were measured in patients with idiopathic dilated cardiomyopathy (N=33) not responsive to more than three months of optimal medical therapy, 18 of whom had associated intestinal malabsorption following gastric bypass surgery for obesity, as well as fifteen normal controls. Serum zinc levels were reduced in both groups with cardiomyopathy compared to controls, suggesting zinc deficiency was not limited to malabsorption. Patients with malabsorption associated DCM also demonstrated lower myocardial zinc content compared with those with idiopathic DCM or controls.

In the prospective portion of this study, 10 of those with malabsorption associated cardiomyopathy received zinc and selenium supplementation (Addamel N 10 mL IV corresponding to Se 300 µg and Zn 13.6 mg every day for 1 week, and subsequently every week for 6 months) in addition to anti-remodeling therapy. The controls were the remaining 8 subjects with malabsorption associated cardiomyopathy who only received anti-remodeling therapy (N=8). Monthly injections improved serum and myocardial zinc content and LVEF (27.6% to 41.7%, $p < 0.001$) an effect that was not seen in the group treated with HF therapy alone. To our knowledge, this is the only prospective study that implicates zinc deficiency in dilated cardiomyopathy and demonstrates improvement with supplementation.

In addition to this insightful study, the authors have previously reported a case of HF attributed to zinc deficiency that improved with improved nutritional status, hormonal blockade and zinc supplementation. (11) Improvement of left ventricular systolic function in our case had halted when anti-remodeling therapy was continued but zinc supplementation was transiently held. Further, two recently completed open label studies evaluated the role for zinc supplementation in two different HF populations (Table 4): a trial of zinc supplementation in patients with non-ischemic HF (n=40), (16) and a trial of micronutrient supplementation (including B vitamins, vitamin D, and zinc) in veterans with systolic dysfunction (n=30). (15) To our knowledge, the results of these studies have not yet been published.

Insights from Micro/Macro Nutrient Supplementation in Patients with HF

Two prospective studies evaluated the role for micro and macro nutritional supplementation, including but not limited to zinc, in patients with ischemic cardiomyopathy. A double blind, randomized control trial compared subjects receiving MyoVive™ (Nutrica International B.V.) to controls. MyoVive supplement mainly contains taurine, coenzyme Q10 and carnitine but also contains 15mg of zinc (150% of daily dietary requirement in adult males). The primary endpoints of the study were myocardial levels of taurine, coenzyme Q10 and carnitine with secondary endpoints including improvement in left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) assessed by radionuclide ventriculography. Subjects receiving nutritional supplementation had an associated decrease LVEDV (171ml to 159 mL, $P<0.05$) but no significant improvement in LVEF and stable LVESV. There was no change in the mean LDEDV in the placebo group (179 to 178 mL) (63) In the second study, 30 subjects with ischemic cardiomyopathy were randomized to multi micronutrient supplement or placebo in a double- blind study. The multi micronutrient supplement contained 15 mg of zinc in addition to selenium, thiamine, coenzyme Q10 amongst other micronutrients. After one year, serum levels of folate and B12 as well as mean LVEF (25.6% to 30.9%; $P<0.05$), the primary endpoint, increased significantly in the

micronutrient group, whereas there was no change in the placebo group. While there was an associated significant improvement in quality of life using EuroQol HG score, there was no improvement in NYHA class in the patients receiving micronutrient therapy. (64) Although unable to isolate the effect of zinc alone, these studies suggest the possible beneficial role of zinc supplementation and require further investigation.

Conclusions and Future Directions

In conclusion, observational data suggest that zinc deficiency may be under evaluated and under recognized in heart failure, in large part because the importance of zinc deficiency has not been emphasized in the literature. Our systematic review of the literature is suggestive of pathobiological pathways linking zinc deficiency to the development and progression of heart failure syndromes. Some available studies are suggestive of the potential therapeutic role of zinc supplementation, which warrants further confirmation in subsequent prospective (ideally randomized) trials.

Limitations

The majority of studies identified in this systematic review were small. Although further investigation is required, we believe the current data are sufficient to raise the possibility of role of zinc deficiency in the development and/or severity of heart failure syndromes and lays the foundation for designing future studies to illustrate this association. Furthermore, most of the data presented in this systematic review are observational and therefore we can only report on associations, rather than confirming causality. Although we provided several pathophysiological mechanisms through which zinc may impact the myocardial function, it could be also hypothesized that zinc is not in the causal pathway of HF but just a marker of incident or recurrent HF. Plasma zinc levels have also not been correlated with nutritional status at the individual level. While serum zinc levels can fluctuate up to 20% within a 24 hour period (65), the lower average levels seen in the HF population in this review are presumed truly reflective of zinc deficiency.

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Disclosure

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Figure 1. Overview of Records Retrieved from Search Strategy (Last search April 2019).

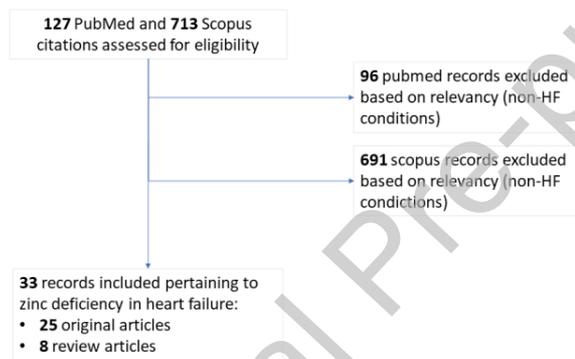


Figure 2. Proposed Structural and Functional Properties of Zinc Related to the Heart.

A) Cytokine modulation. Zinc positively mediates gene expression of interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) and negatively tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta) and interleukin-8 (IL-8), deficiency leads to impaired immunity and increased inflammation.

B) Cellular effects. Via interacting with calcium transport through L-type channels, it has electrical and mechanical effects on cardiomyocytes. Zinc reduces the activity of TNF-alpha and caspase 3, thereby preventing apoptotic signals. It is also thought to be protective for cardiac

stem cells, required for the healing process in the event of injury and is a cofactor in matrix metalloproteinases.

C) Oxidative stress reduction. Zinc is a co-factor for nitric oxide synthase, a key component of endothelial health and vasodilation. Importantly, zinc is a critical part of superoxide dismutase, thereby reducing the superoxide anions and the oxidative stress from cells.

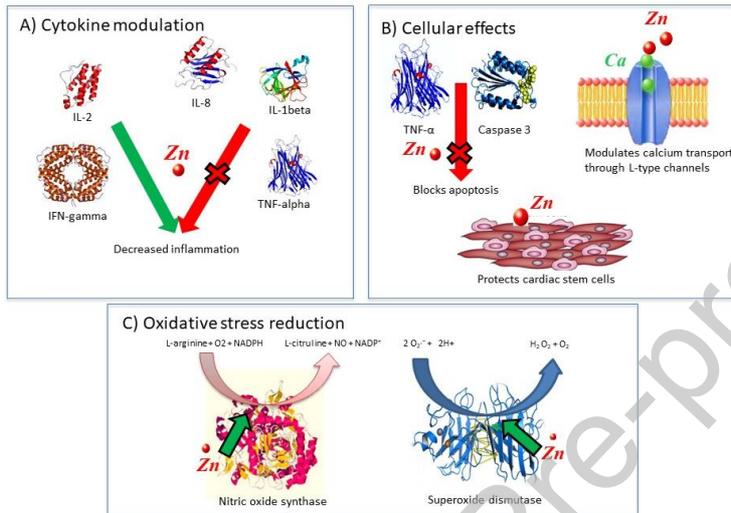


Figure 3. Causes of Serum Zinc Deficiency in Heart Failure.

Low serum zinc levels in patients with heart failure can be caused by reduced dietary intake, reduced absorption, increased uptake in stressed tissues, and increased excretion.

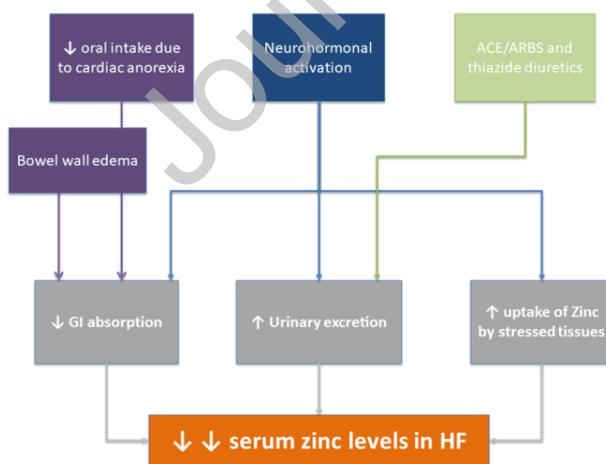


Table 1: Search Strategy for Potentially Relevant Studies from January 1940 to January 2017

1. PubMed search: (zinc[Mesh] OR zinc*[TI] OR zn[TI] OR (("Micronutrients"[Mesh] OR "Trace Elements"[Mesh]) AND (zinc[TIAB]))) AND ("Cardiomyopathies"[MAJR] OR "Heart Failure"[MAJR] OR cardiomyopathy*[TI] OR (heart* AND failure*[TI]))
2. Scopus search: zinc AND "heart failure" limit to title, abstract, keywords
3. Cochrane Database of Systematic Reviews search: zinc AND "heart failure"
4. Clinicaltrials.gov search: zinc AND (heart OR cardiac OR cardiomyopathy OR heart failure)

Table 2: Studies Reporting Deficient Nutrient Intake and/or Zinc Intake in HF.

First author	Year	Study Design	Population/N	Summary
McKeag (66)	2017	Cross sectional	79 patients with NYHA class II and III chronic HF	Mean intake of zinc was 8.7 ± 3.7 mg/d. 31% of subjects consumed less than the recommended reference intake.
Hughes (37)	2012	Cross sectional	67 participants including 39 subjects with HF, compared with 27 healthy controls	65% of the HF population consumed less than the reference nutrient intake for zinc, however there was no significant difference in the consumption of zinc between the controls and HF group (10.4mg/d in controls vs 8.5mg/d in NYHA II vs 8.9 mg/d in NYHA III/IV, P=0.21) .
Frediani (34)	2013	Cross sectional	114 subjects with NYHA class II and III HF	Subjects following sodium restriction to <2000mg/d consumed significantly less micronutrients including zinc compared to those consuming more than 2000mg sodium/day (57.2% vs 74.7%, P<0.002).
Lourenco (33)	2009	Cross sectional	125 patients with HF	40% of men and women with HF had inadequate intake of zinc (less than estimated average requirement 9.4mg/d for men and 6.8mg/day for women).
Gorelik (67)	2003	Cross sectional	57 hospitalized patients with HF vs 40 similar patients without HF	Intake of zinc was poor in both groups, fell short of recommended intake levels however was comparable between the two groups (5.7mg/d vs 5.6 mg/d, P=NS)

Abbreviations: HF= heart failure , NYHA= New York Heart Association

Table 3: Original Articles on Serum Zinc Levels in HF

First author	Year	Study Design	Population/N	Summary	Comment
Yoshihisha	2018	Longitudinal	968 patients	Average zinc level was	(12,19)

(32)			with decompensated HF who had serum zinc levels checked at hospital discharge.	68 ± 16mcg/dL. Those with zinc levels <62mcg/dL were older, had significantly higher systolic BP, more often had CKD and had increased use of diuretics. On CPET peak VO ₂ was lower and VE/VCO ₂ was significantly higher. In Kaplan Meier analysis, patients with Zinc levels < 62mcg/dL had significantly increased cardiac mortality (P=0.001) and all-cause mortality (P<0.001).	
Melnikov (17)	2015	Cross sectional	47 participants, including patients with idiopathic DCM, ICM, HCM, and controls	Zinc levels in the control group (130 ± 21 mcg/dL) were lower than that in patients with idiopathic DCM (158 ± 73 mcg/dL, P=(30)0.03), but comparable with patients with ICM (133 ± 53 mcg/dL, P=0.42) and HCM (142 ± 33 mcg/dL, P=0.33).	Contradictory to majority of literature, also control values are higher than what is reported in other studies
Alexanian (30)	2014	Cross sectional	125 patients with HF and 21 controls without HF	Plasma zinc levels in the control group (88 ± 18 mcg/dL) were significantly higher than that in patients with acute HF (74 ± 16 mcg/dL, P<0.001) or chronic HF (82 ± 20 mcg/dL, P=0.04). Moreover, serum zinc levels were significantly lower in acute HF than in chronic HF (B = -8.670, 95 % CI -15.593 to -1.747, p = 0.015).	
Frustaci (12)	2012	Longitudinal	18 patients with intestinal malabsorption following gastric bypass surgery for obesity, and associated	Patients with malabsorption-associated DCM had lower plasma zinc (75 ± 12 mcg/dL) compared with patients that had idiopathic DCM (113 ±	

			DCM, 15 patients with idiopathic DCM, and 15 controls	23 mcg/dL, $P<0.05$) or controls (126 ± 54 mcg/dL, $P<0.05$). Patients with malabsorption-associated DCM also represented lower myocardial zinc content compared with those with idiopathic cardiomyopathy or controls. Among those with malabsorption-associated DCM, monthly injections with zinc and selenium ($n=10$) improved serum and myocardial zinc content and was associated with improvement in left ventricular systolic function, an effect that was not seen in those receiving heart failure therapy alone ($n=8$).	
Ghaemian (19)	2011	Cross sectional	78 patients with advanced HF with reduced EF and 40 controls	Patients with HF with reduced EF had markedly lower zinc levels compared with controls (HF with AF 23 ± 17 mcg/dL vs. HF without AF 25 ± 28 mcg/dL vs. control 71 ± 22 mcg/dL, $P<0.001$).	Profound zinc deficiency of the HF patients could be explained by nutritional deficiencies, high NYHA class, and use of ACEi and ARBs
Shokrzadeh (20)	2009	Cross sectional	30 patients with ICM and 27 healthy individuals	There was no difference in zinc levels between patients with ICM (105 ± 28 mcg/dL) and healthy controls (112 ± 42 mcg/dL, $P=0.42$). There was a trend towards lower zinc levels in NYHA class III compared with class II CHF (95 ± 27 mcg/dL vs. 127 ± 29 mcg/dL, $P=0.14$).	This study had subjects with lower NYHA class (average 2.5) compared to the above, and fewer patients were on ACEi/ARB.
Salehifar	2008	Cross	18 patients with	Patients with DCM had	Majority were

(21)		sectional	DCM and 27 healthy individuals	non-significantly lower zinc levels compared with healthy controls (97 ± 25 mcg/dL vs. 112 ± 42 mcg/dL, $P=0.3$).	NYHA class III
Trasobares (22)	2007	Cross sectional	11 patients with decompensated HF (being treated with ACEIs and diuretics) and 24 healthy controls	Serum zinc levels were lower in patients with HF receiving ACEIs compared with healthy controls (62 mcg/dL vs 87 mcg/dL, $P=0.001$). Urine zinc levels were higher in patients with HF compared to controls (2.24 vs 0.21 mcg/g creatinine, $P<0.001$).	
Arroyo (23)	2006	Cross sectional	30 African Americans with acute decompensated HF (subdivided by two groups of 15 based on symptoms onset), as well as 10 African Americans with stable HF and 9 African American healthy controls	Both subgroups of patients with HF had low zinc levels compared with reference lab value at the study ($75-140$ mcg/dL). In HF long term vs HF short term, serum zinc levels were 67 ± 5 mcg/dL vs. 66 ± 3 mcg/dl, vs. 74 ± 3 mcg/dl in asymptomatic compensated HF. Specific numbers for healthy controls are not reported. Only HF short term was statistically significant ($P<0.05$).	
Kosar (31)	2006	Cross sectional	26 patients with idiopathic DCM, 28 patients with ICM and 30 healthy controls	Mean serum zinc did not differ between types of HF but was significantly lower in both patients with idiopathic DCM and ICM compared with controls (55 ± 10 mcg/dL vs. 62 ± 13 mcg/dL, $P<0.01$).	
Topuzoglu (24)	2003	Cross sectional	54 patients with dilated cardiomyopathy and 20 healthy controls	Patients with dilated cardiomyopathy had lower zinc levels compared with healthy controls (81 ± 15 mcg/dL vs. 93 ± 23 mcg/dL, $P<0.001$).	
de Lorgeril	2001	Cross	21 patients with	Mean zinc levels for	

(14)		sectional	HF (18 ICM, 3 idiopathic DCM) and 18 controls.	subjects with HF (82 ± 12 mcg/dL) was significantly less than controls (90 ± 9 mcg/dL, $P < 0.05$).	
Ripa (25)	1998	Cross sectional	15 patients with DCM, 11 patients with hypertrophic cardiomyopathy, and 25 controls	Compared with controls (105 ± 13 mcg/dL), patients with DCM (87 ± 12 mcg/dL) and HCM (96 ± 10 mcg/dL) had lower zinc levels ($P < 0.05$ for both).	
Chou (68)	1998	Cross sectional	32 patients with DCM and 31 matched controls	No significant differences in mean serum zinc values between patients with DCM and controls (87 ± 38 vs 77 ± 12 mcg/dL).	
Cenac (28)	1996	Cross sectional	35 patients with peripartum cardiomyopathy compared with 40 women living under same conditions	Mean zinc levels for subjects with peripartum cardiomyopathy (90 ± 21 mcg/dL) was significantly lower than that of controls (117 ± 25 mcg/dL, $P < 0.001$)	
Golik (27)	1993	Cross sectional	15 patients with T2DM and HF, 9 patients with isolated HF, and 20 patients with isolated T2DM	Zinc levels were comparable in patients with T2DM and HF (86 ± 15 mcg/dL), isolated HF (75 ± 10 mcg/dL), and isolated T2DM (105 ± 22 mcg/dL).	
Oster (26)	1993	Cross sectional	20 patients with DCM and 50 controls	Patients with DCM had lower zinc levels compared to controls (75 ± 20 mcg/dL vs 93 ± 18 mcg/dL, $P < 0.01$)	
Atlihan (69)	1990	Cross sectional	Children with and without HF	The mean zinc levels for patients with HF was significantly less than that of controls (93 ± 19 mcg/dL vs. 108 ± 16 mcg/dL, $P < 0.05$).	
Burguera (70)	1988	Cross sectional	8 chagasic HF patients compared to 29 controls	Zinc levels significantly lower in chagasic patients compared with controls (64 ± 2 vs $70 \pm$	

				2, P<0.05)	
Smetana (71)	1987	Cross sectional	30 patients with idiopathic DCM and 30 patients with CAD	Serum zinc concentrations were significantly less in patients with idiopathic DCM compared with patients with CAD (70 ± 10 vs 109 ± 19 , P<0.001).	

Abbreviations: ACEi= angiotensin-converting enzyme inhibitors, AF= atrial fibrillation, ARB= angiotensin receptor blocker, CAD = coronary artery disease, CKD = chronic kidney disease, CPET= cardiopulmonary exercise testing, DCM=dilated cardiomyopathy, EF = ejection fraction , ICM= ischemic cardiomyopathy, HCM= hypertrophic cardiomyopathy, NYHA= New York Heart Association, T2DM= Type II Diabetes Melitus, VE/VCO₂= minute ventilation/carbon dioxide production ratio, VO₂= rate of oxygen consumption

Table 4: Ongoing Trials Evaluating Zinc Supplementation in HF

Institution	Year	Study Design	Population/N	Summary
University of Michigan	2012	Longitudinal/completed	40 patients with nonischemic DCM	Patients received zinc supplementation for ten months.
Phoenix VA Health Care System	2016	Longitudinal/completed	30 veterans with systolic dysfunction	Micronutrient supplementation (including B vitamins, vitamin D and zinc) for six months. Follow up at baseline 3, 6, 12 months.

Abbreviations: DCM= dilated cardiomyopathy