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Nutritional and Anti-Inflammatory Interventions in Chronic Heart Failure

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Summary

Five million individuals with chronic heart failure (CHF) in the United States have poor clinical outcomes including high death rates. Observational studies have indicated a reverse epidemiology of traditional cardiovascular risk factors in CHF; in contrast to trends seen in the general population, obesity and hypercholesterolemia are associated with improved survival. The temporal discordance between the overnutrition (long-term killer) and undernutrition (short-term killer) not only can explain some of the observed paradoxes but also may indicate a role for malnutrition, inflammation and oxidative stress that result in cachexia contributing to poor survival in CHF. Diminished appetite or anorexia may be both a cause and a consequence of this so-called malnutrition-inflammation-cachexia (MIC) or wasting syndrome in CHF. Neurohumoral activation, insulin resistance, cytokine activation and survival selection resultant genetic polymorphisms may also contribute to the prominent inflammatory and oxidative characteristics of this population. In CHF patients with wasting, nutritional strategies may be a promising therapeutic approach in CHF, especially if the provision of additional protein and energy also includes nutrients with anti-inflammatory and anti-oxidant properties. Regardless of the etiology of anorexia, appetite stimulating agents especially with anti-inflammatory properties such as megestrol acetate or pentoxifylline may be appropriate adjuncts to dietary supplementation. Understanding the factors that modulate the MIC and wasting and their associations with clinical outcomes in CHF may lead to the development of nutritional strategies that alter the pathophysiology of CHF and improve outcomes

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Keywords

Malnutrition-inflammation-cachexia (MIC); chronic heart failure; protein-energy malnutrition; wasting; reverse epidemiology

CHF Patients and Poor Outcome

In the United States, there are currently approximately five million individuals with chronic heart failure (CHF).^{1,2} CHF is the only major cardiovascular (CV) disease with rising incidence and prevalence in past decades. The life-time attributable risk for CHF for men and women is approximately 1 in 5. Increasing age of the population, greater awareness, and improved diagnostic techniques for the detection of CHF may have contributed to the steady rise in incidence.³⁻⁵ Another reason for the rising incidence of CHF is improved treatment and survival of patients with ischemic heart disease, the most common etiology of CHF.³⁻⁶ CHF is characterized by a high rate of hospital readmission and death, significant functional compromise, reduced health related quality of life (QoL), and increased caregiver burden.⁷⁻⁹ Data from the *National Health and Nutrition Examination Survey (NHANES)* indicated that 72% of men and 60% of women aged 65 to 74 years died within 10 yrs of their self-reported onset of CHF.^{7,10} Increased severity of CHF, as measured by the *New York Heart Association (NYHA)*, is associated with higher mortality risk.^{11,12} The increased CHF prevalence represents an enormous burden to our health care system when coupled with extended and frequent hospital stays and poor HRQOL and survival.¹⁻⁵

Improving Clinical Outcomes in CHF Patients

Because most CHF patients die prematurely and because their death is attributed to CV disease states, efforts to improve traditional CV risk factors might appear promising. Indeed, the known CV risk factors, i.e. hypercholesterolemia, hypertension and obesity, are associated with independently increased risks for *developing* CHF and mortality in the general population.^{13,14} Hence, it would be reasonable to infer that once CHF develops, these CV risk factors would continue to be associated with increased mortality. However, there has been increasing data indicating that in CHF patients, conventional CV risk factors are *not* positively associated with mortality risk (see below).

Therapy with angiotension converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and β -blockers are well studied and widely available treatment modalities that ameliorate symptoms, reduces morbidity, and improve survival in CHF patients.^{6,15} Aldosterone antagonists improve survival in patients with moderately-severe to severe symptoms as well.^{15,16} However even among CHF patients who receive evidence based medical therapy CHF mortality has remained unacceptably high. Hence, additional and/or novel therapeutic alternatives that are safe and practical should be sought and examined to ascertain whether they can improve poor CHF survival.

The Concept of Reverse Epidemiology

Many reports indicate that there is a high prevalence of body wasting and cachexia in CHF.^{17–21} CHF patients with cachexia have an extremely high death rate, i.e., up to 50% over 18 months,²² a mortality worse than many cancers. In industrialized and affluent countries, undernutrition and cachexia are *uncommon* cause of poor outcome in the general population, whereas “*over-nutrition*” is associated with a greater risk of CV and other diseases and leads to shortened survival.²³ In contrast, in CHF patients “*undernutrition*” and wasting are common and strong risk factors for death.²¹ Consistent with this notion, most epidemiologic studies have shown survival advantages of obesity in CHF patients (Figure 1).²⁴ The terms “reverse epidemiology” or “obesity paradox” underscore such paradoxical observations.^{25–27} These terms indicate that certain markers which predict a low likelihood of CV events and indeed an improved survival in the general population, such as low body mass index (BMI), low blood pressure, and low serum cholesterol, become paradoxically strong risk factors for increased morbidity and mortality in CHF patients. Moreover, some indicators of over-nutrition such, as obesity and hypercholesterolemia, actually predict improved outcome in CHF patients.^{25,28} In fact, observational studies of CHF patients have shown that weight gain is associated with improved survival while weight loss is associated with markedly increased mortality risk (unpublished data of S.D. Anker).

The reverse epidemiology phenomenon is not unique to CHF population. Patients with renal failure undergoing maintenance hemodialysis (MHD)²⁵, geriatric populations,^{29,30} patients with rheumatoid arthritis,³¹ AIDS,³² chronic pulmonary disease,³³ or malignancy,³⁴ and possibly several other vulnerable populations with chronic disease states may have similar risk factor reversals.^{25,35,36} Hence, the key to improved survival in CHF patients and other similar populations may lie in interventions that modulate conditions related to the reverse epidemiology phenomenon. And although counterintuitive, the obesity paradox is supported by a growing body of medical literature.

Anorexia and Malnutrition in CHF

Diminished appetite and inadequate food intake, together known as anorexia, may be engendered in CHF as a consequence of clinical symptoms such as fatigue and dyspnea, or via intestinal edema causing nausea, diminished absorption, and protein-losing enteropathy.^{37–43} Anorexia might also be an iatrogenic consequence of drug therapy, e.g., digoxin.³⁷ Decreased food intake may also be a result of imposed dietary restrictions.⁴⁴ CHF patients with cachexia appear to suffer from gastrointestinal fat malabsorption but not from gastro-intestinal protein loss.⁴⁵ Another important aspect is a significantly higher resting metabolic rate in CHF patients,^{46–48} which increases with the CHF severity^{48,49}. Nutritional intake that may have been adequate prior to developing CHF may be inadequate after CHF is established. Finally, the robust, systemic inflammatory activation characteristic of CHF may lead to anorexia, similar to what has recently shown in dialysis patients.^{50–55}

The term *malnutrition*, even though may be used for both inadequate and excessive nutrition, generally indicate conditions related to *under-nutrition*. Malnutrition may be related to *macronutrients*, i.e., the protein and energy malnutrition, or *micronutrients* such as vitamins

and minerals including trace elements. The protein-energy malnutrition can be defined as the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, which is caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which can potentially be improved by nutritional repletion.⁵⁶ Hence, the protein-energy malnutrition is engendered when the body's need for protein or energy fuels or both cannot be satisfied by the current dietary intake. Although various studies using different criteria have been used to establish the presence of protein-energy malnutrition in the CHF population, its exact prevalence is not known, but it is estimated between 20% and 70% depending on assessment criteria.

Per definition the protein-energy malnutrition should not involve micronutrients; however, many protein-energy malnourished CHF patients may also have a relative deficiency in vitamins and minerals. Moreover, it is important to appreciate that, even though cachexia traditionally relates to weight loss, there is no clear-cut separation between malnutrition and cachexia in CHF patients, especially since inflammation, oxidative stress or other conditions may lead to both in CHF patients (see below). Furthermore, even among CHF patients who fall into an overweight or obese category by body mass index, evidence of malnutrition, such as hypoalbuminemia, may still be present.⁵⁷⁻⁵⁹ Hence, a cross-sectional body size measure may be misleading.

Chronic Inflammation

An important and inadequately appreciated feature of malnutrition and wasting in CHF is the presence of chronic inflammation.⁶⁰⁻⁶³ Tumor necrosis factor alpha (TNF- α) is significantly increased in CHF associated with cachexia⁶⁴ as in the cases of cachectic patients with a variety of cancers, infections, renal failure or vascular diseases.^{52,65,66} The effect of TNF- α on wasting might be mediated by effects on endothelium or on the control of apoptosis.⁶⁷ The chronic inflammatory state may result from bacterial or endotoxin translocation enhanced by bowel-wall edema.⁶⁸⁻⁷¹ Inflammation may be responsible for the wasting syndrome and hypoalbuminemia in CHF.⁷²⁻⁷⁵ It has also been postulated that lower body weight is associated with a heightened catabolic state, which is associated with higher levels of TNF- α and other cytokines, as well as increased cortisol/dehydroepiandrosterone balance.^{76,77} Hence, nutritional interventions with anti-inflammatory and anti-oxidant properties may be more effective in CHF patients than the mere provision of protein and energy.

Cardiac Cachexia and Malnutrition-Inflammation Complex

According to the literature, 20% to 30% of CHF patients have hypoalbuminemia <3.5 g/dL and up to 70% have muscle atrophy.⁵⁷⁻⁵⁹ We recently showed that hypoalbuminemia is associated with a 2-fold increase in death risk in a group of CHF outpatients.⁵⁹ Although "cardiac cachexia" (CC) traditionally implies the presence of extreme wasting in the setting of CHF, more inclusive definitions of CC have recently been evolving, according to which any significant weight loss or signs of protein-energy malnutrition and inflammation such as hypoalbuminemia are included. Anker et al defined CC as 6% loss in edema-free weight over at least 6 months²⁰. Some investigators have proposed other terms such as malnutrition-

inflammation-cachexia (MIC) or wasting syndrome²¹ which has also been used for a chronic renal failure associated cachexia, also known as Kidney Disease Wasting.⁵⁶ Another analogous condition is the “cancer anorexia-cachexia syndrome” (CACS), which is described for malnutrition and wasting in malignancies.^{78,79} No matter what nomenclature is used, malnutrition and inflammation are both strong predictors of increased mortality in CHF patients and other similar populations ; furthermore, it is likely that similar pathophysiologic mechanisms of wasting are at play in all these chronic disease states (Figure 2).^{21,22,56}

Oxidative Stress (SOX) and MIC in CHF

Oxidative stress (SOX) implies the potential of tissue damage from an imbalance between an excessive generation of oxidant compounds and insufficient anti-oxidant defense mechanisms.^{80,81} The generation of oxidative compounds represents part of the defense mechanisms against invading microorganisms and malignant cells, as well as of tissue healing and remodeling.⁸¹ However, an improper or maladaptive activation of oxidative processes may be chronically present in pathological situations including in CHF patients.^{82–86} Several deficiencies in different components of the anti-oxidant defense mechanisms may be responsible for the CHF associated SOX.^{86–91} Reduced intake and reduced levels of vitamin C and some other anti-oxidant vitamins are probably due to anorexia and malnutrition.^{88,92,93} At the same time, pro-oxidant activity is increased in CHF patients due to advanced age, higher prevalence of diabetes, circulating endotoxin, and chronic inflammation.⁸⁶ Blood levels of several lipid and protein oxidation products such as F2-istoprostanes are increased in CHF patients.^{94,95} SOX may also promote formation of advanced glycation end-products (AGEs) independently of glucose levels.^{96–98} Hence, the SOX resultant “carbonyl stress” products may also be associated with further damage in CHF.^{99,100}

Anti-Oxidants Interventions in CHF

Several clinical observations indicate that SOX play a role in human heart failure, although to date the clinical data have been conflicting.^{82,101,102} Treatment with vitamin C inhibits endothelial cell apoptosis in CHF.¹⁰³ Anti-inflammatory interventions may mitigate SOX in CHF.¹⁰⁴ The superiority of carvedilol to other β -blockers in CHF may be in part due to its antioxidant effects.^{105–107} However, large clinical trials of the antioxidant vitamins have not shown benefit in preventing morbidity or mortality in the general population or in those at risk of cardiovascular disease.^{108–110} The mixed and often negative results of clinical trials using antioxidant therapy may also reflect the lack of effectiveness of a *single* anti-oxidant agent;¹¹¹ an integrated approach using more than one anti-oxidant component, especially in combination with anti-inflammatory and nutritional interventions, focusing on malnourished CHF patients, may hold more promise.¹⁰⁴

The Endotoxin-Lipoprotein Hypothesis

A low serum cholesterol is not only a predictor of poor outcome in CHF patients^{21,112,113} but also in other disease states characterized by inflammation and SOX, such as malignancy,

AIDS and renal failure,^{25,35,60,114–117}. Serum cholesterol is a surrogate of the *totality of lipoproteins*. Freely circulating lipopolysaccharides (LPS) activate pro-inflammatory cytokine cascade leading to the MIC/SOX complex^{69,118,119}. Hence, intact (not oxidized) lipoproteins may be a *defense mechanism* against inflammation by binding to and neutralizing the circulating LPS.^{70,120} Higher levels of endotoxins have been observed in both CHF and dialysis patients.^{118,119,121,122} Hypothetically, in malnourished or inflamed CHF patients with a *low* cholesterol level or *dysfunctional* lipoproteins, the LPS bioactivity can practically increase even without more absolute LPS on board, leading to pro-inflammatory cytokine activation cascade^{21,123}, esp. in the setting of pro-inflammatory genetic polymorphism (see below).

The Temporal Discordance Hypothesis

In contrast to the conventional CV risk factors and over-nutrition that require several years to decades to exert their deleterious effect, the impact of wasting and MIC appears rapid, resulting in decreased short-term survival.⁵ This “time discrepancy” or *temporal discordance* between the two sets of competing risk factors, i.e., over-nutrition as the long-term killer vs. under-nutrition as the short-term killer, may explain the clinical relevance of the *reverse epidemiology* phenomenon observed in CHF patients, in whom the under-nutrition overwhelms the presence of over-nutrition, leading to poor short-term survival.^{25,36} (Figure 3) Hence, no matter how strongly such CV risk factors as hypercholesterolemia or obesity are present, CHF patients will continue to die excessively and fast as long as the short-term impact of cachexia and MICS prevails. In other words, underweight CHF patients will not live long enough to die of obesity, hypercholesterolemia or hypertension, because they die much faster of cachexia.³⁶ Hence, if the main issue is indeed the high rate of *short-term mortality*, it is also expected that *short-term interventions* to correct the underlying condition, i.e., the MIC/SOX complex, can improve survival. Based on this plausible hypothesis, nutritional interventions may be promising.

Gene Polymorphism and MIC in CHF Patients

The great inter- and intra-individual variability in the prevalence of cachexia and MIC/SOX complex in CHF patients, which cannot be explained by inflammatory or oxidative factors alone, indicates that genetic differences may be involved. Many individuals with atherosclerotic heart disease die before they reach CHF. Thus, we hypothesize that a significant “survival selection process” leads to a higher prevalence of certain genotypes with higher prevalence of MIC/SOX amongst the survivors, i.e., the full-blown and yet surviving CHF patients. This hypothesis may also explain why the traditional cardiovascular risk factors are less relevant or even paradoxical in CHF patients, whereas such non-traditional factors as the MICS/SOX complex emerge as the strongest survival predictors.

A substantial heritability (35–40%) for CRP and albumin levels and leukocytes have been reported in non-CHF populations with heart disease.¹²⁴ Similarly, individual factors may significantly influence the levels of inflammatory markers in CHF and dialysis patients¹²⁵. The example of Asian dialysis patients may be illuminating: Because dialysis patients of Asian origin have a lower CRP levels and better survival,¹²⁶ it could be argued that either

the Asian diet or genetic factors or both may account for the observed differences. Indeed, Szalai et al¹²⁷ reported that the prevalence of a polymorphic GT-repeat in the intron of the CRP gene, which contributes to variations in baseline CRP, was 2-fold higher in Caucasians than in African Americans. Thus, single nucleotide polymorphisms (SNPs) in cytokine genes may have a significant influence on inflammation and its attendant morbidity in CHF patients as well. Although genetic factors such as SNPs may have a modest effect at an individual level, because of their presumably high frequency in the CHF population (see above our “survival selection” hypothesis above), these genetic variants can be associated with a high attributable risk of cardiovascular disease and death.

Can Nutritional Interventions Correct Wasting, Inflammation and SOX?

To the best of our knowledge, nutritional interventions to prevent or ameliorate the MIC/SOX complex in CHF have been rarely, if ever, studied. Two recent studies based on nutritional interventions using unconventional vegetarian¹²⁸ or Mediterranean-style¹²⁹ diets showed that diet might be effective in correcting inflammation and associated CV risk in non-CHF populations. Many foods contain factors that can modulate the synthesis or activity of pro-inflammatory mediators^{51,130}. The efficacy of dietary *fish oil* has been demonstrated in several studies.^{91,131–135} Fish oil is an abundant source of *eicosapentaenoic acid* (EPA), a precursor of certain prostaglandins and leukotrienes with anti-inflammatory properties.^{136–138} In addition, *borage oil*, a plant seed with a high concentration of *gamma linolenic acid* (GLA) has anti-inflammatory, anti-oxidant and vaso-protective properties.^{139–144} GLA is elongated to dihomo-gamma-linolenic acid (DGLA), the fatty acid precursor to prostaglandin E1, known to have vasodilator and anti-aggregator properties.^{143,145} *Carnitine* is another nutraceutical that mitigates pro-inflammatory cytokine levels in patients with liver disease¹⁴⁶ and heart failure¹⁴⁷ and in dialysis patients,^{147–149} although it may not be effective in CHF. Recently, a commercially available nutritional supplement that contains relatively large proportions of fish oil, borage oil, carnitine and other anti-oxidants and is designed for critically ill patients with inflammation and SOX^{137,138,150,151} corrected hypoalbuminemia in a small group of malnourished dialysis patients in a non-randomized pilot study.¹⁵¹ However, this or similar nutritional supplements have not yet been tested in CHF patients.

Nutritional Interventions for CHF

A number of different modalities can be employed to improve nutritional, inflammatory and oxidative status in CHF patients, as listed in Table 1. Among more intensive modalities, tube feeding and parenteral interventions are cumbersome, invasive, and cannot be imposed to the average CHF outpatient. Hormonal interventions including growth hormones (such as IGF-I)^{152,153}, ghrelin^{154–159}, and melano-cortin antagonists^{55,160,161} have been under investigation, but some of their related studies in CHF have yielded mixed results.^{37,90,154,162} With Regard to ghrelin and melanocortin antagonists, further research will be necessary to identify the exact pathways involved, to examine their safety profile in human subjects with CHF, and to find the best therapeutic strategies of using these agents. Some appetite stimulants and anti-inflammatory/anti-oxidant agents appear promising for use in CHF patients. Nevertheless, as we have recently discussed for dialysis patients, who

have a similar conundrum,^{5,163,164} it is less likely to find one single agent (e.g., fish oil alone or vitamin E alone) to correct MIC. *Integrated* oral supplements, especially if they contain a combination of several nutritional, anti-inflammatory and anti-oxidant agents and provide supplemental protein and energy, are more promising modalities.

Can Oral Interventions Correct MIC and Improve Survival in CHF?

To date there are no large-scale, randomized prospective interventional studies that have examined this question. According to some reports, aggressive attempts to increase nutritional intake may improve nutritional or clinical status in CHF patients.^{38,39,87,165–168} However, achieving a moderate increase in food intake without concurrent provision of anti-inflammatory or anti-oxidant nutrients may not be successful. The clinical potential of improving nutritional status in CHF patients with MIC/SOX by means of oral nutritional therapies should be demonstrated in well-designed clinical trials. However, before large-scale and expensive trials are launched, smaller pilot/feasibility studies are needed.

Anti-Inflammatory and Anti-Oxidant Agents

Although epidemiologic evidence links wasting to inflammation and SOX and to poor outcome in CHF patients, there are no randomized trials to indicate improvement of nutritional status or clinical outcome by simple oral nutritional supplements with anti-inflammatory and antioxidant properties. A number of treatment modalities have been implicated to target inflammation and/or SOX in CHF patients. (Table 2) These include existing and emerging CHF therapies ACE inhibitors,¹⁶⁹ ARB, carvedilol, and statins.^{170–172} Antioxidant vitamins including vitamin E^{173–176} and vitamin C^{177–183} have also been suggested as potential treatments for CHF, even though some recent randomized trials including HOPE fail to show any beneficial effect.¹⁰⁹ There are however discrepancies, for instance, pertaining to the role of vitamin E in survival in both CHF patients¹⁷³, coronary heart disease, and in the general population^{110,184}. More directly targeting the myocardium and vasculature with potent antioxidant therapies may be necessary in order to derive therapeutic benefit.

Orexigenics

Among appetite stimulants that are studied clinically (Table 3), *megestrol acetate* (MA) is by far the most utilized and best-studied agent, although not among CHF patients. MA, 800 mg/day, increases appetite and food intake in cancer or AIDS patients.^{185–189} MA reduces the in vitro production of cytokines and serotonin in peripheral blood mononuclear cells of cancer patients, down-regulates the synthesis and release of pro-inflammatory cytokines, and mitigates SOX.^{34,190–195} However, there are some serious concerns about adverse effect of MA. There are virtually no studies concerning MA in CHF patients, although our group¹⁹⁶ and others^{197–200} have used MA in dialysis patients. An increase in serum albumin and weight gain can be observed, but increase in fat mass appears to be the dominant feature.^{196,198} MA is associated with many side effects including thrombotic events, diarrhea, confusion/hallucinations, hyperglycemia, headache and dizziness, elevated LDH, Cushing syndrome, and cerebrovascular accident and anti-testosterone effects in

men^{197,201–205}. Hence, it appears doubtful whether MA will be used routinely in low risk and stable CHF patients without extreme wasting given its unfavorable side effect profile.

Pentoxifylline

Pentoxifylline (PTX) is a tri-substituted xanthine derivative. Due to its hemorrheologic and anti-platelet properties, PTX has been safely used for 3 decades to treat peripheral vascular disease.^{206–210} PTX down-regulates local pro-inflammatory cytokine-mediated NO synthase pathway,²¹¹ inhibits TNF- α and nuclear factor kappa B (NF- κ B) production,^{212–215} and decreases body weight loss and muscle protein wasting in acutely ill patients.²¹⁶ The anti-TNF- α and orexigenic properties have rendered PTX a promising agent for treating rheumatoid arthritis and cancer anorexia/cachexia,^{213,217–222} as well as to treat the MIC complex and anemia in dialysis patients.^{223,224} PTX attenuates cardiac dysfunction and reduces TNF- α and NF- κ B levels in ischemic-reperfused heart.²²⁵

The anti-inflammatory and cardioprotective effect of PTX may improve clinical outcomes in CHF patients with cachexia. To our knowledge, only 2 groups have conducted RCTs to compare PTX with placebo in CHF patients. Sliwa and colleagues from South Africa have reported 4 clinical trials (PTX 400 mg tid for up to 6 mo vs. placebo) in 18 to 49 black African patients (total of 144 subjects) and reported improved ejection fraction and reduced plasma cytokine levels^{226–233}. Bahrmann et al²³⁴ conducted a similar RCT in 47 subjects in Germany (PTX 600 mg bid) and did not find any difference in two groups after 6 months. Both South African and German studies had serious methodological and analytic limitations and did not target patients with MIC or wasting, nor did they measure nutritional parameters and appetite in studied subjects. Moreover, these studies did not examine the effect of PTX *combined* with nutritional supplements. It is possible that PTX alone cannot correct the catabolic state in CHF, whereas its combination with nutritional supplements with anti-inflammatory and anti-oxidant ingredients may have synergistic effects.

Conclusions and Future Steps

The poor clinical outcomes in patients with established CHF may not be addressed by targeting traditional cardiovascular risk factors of obesity, hypercholesterolemia, and hypertension. Malnutrition and inflammation are both strong predictors of increased mortality in CHF patients. Addressing these factors has the potential to improve outcomes. Nutritional intervention may be an effective means to that end. The National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health has recently issued a new program announcement (PA 05-089) to encourage investigators to examine nutritional avenues in CHF patients.

A complex set of conditions that are related to the cachexia, inflammation and oxidative stress may be the etiology of the risk factor reversal or reverse epidemiology and high death rate in CHF patients. The short-term death risk due to undernutrition overwhelms the long-term effects of overnutrition leading to poor survival in malnourished and/or cachectic CHF patients. If our foregoing hypotheses are true, then the key to improving survival in heart failure patients as well as in other 20 to 30 million Americans with other disease processes

exhibiting a reverse epidemiology may be nutritional interventions that can correct MIC. If a drop in weight over time is associated with poor outcome in CHF patients and if weight gain confers improved survival, nutritional interventions esp. with anti-inflammatory and anti-oxidant properties may be the most promising alternatives. However, since the wasting process in CHF is multi-factorial, narrowly-targeted therapeutic strategies are not likely to be successful. Integrated nutritional interventions that target several aspects of the MIC and wasting in form of combined nutritional treatment strategies with novel micronutrient components that have anti-oxidant and anti-inflammatory properties may be a solution and need to be tested. Appetite stimulating agents especially with anti-inflammatory properties such as MA or anti-inflammatory agents such as PTX may be appropriate adjuncts to dietary supplementation in CHF patients.

The ongoing focus with treating such conventional risk factors as hypertension, hypercholesterolemia, and obesity utilizing treatment targets derived from community cohorts are not likely to lead to an immediate improvement of high mortality rate in CHF patients, as long as the short-term survival is the issue at hand. Such practices as imposing “ideal” BMI ranges based on the general population norms or mandatory weight loss programs for heart transplant wait-listed patients may need to be reevaluated. Dismissing the theory of Reverse Epidemiology as counterintuitive and potentially harmful may not be the most scientifically rigorous approach in dealing with this conundrum. The characteristics of a surviving CHF patient stand in a clear contradiction to those predicted by traditional cardiovascular risk factors. For CHF patients it may be time to go beyond the traditional framingham risk factors and try to explore new paradigms and novel modalities such as nutritional interventions that can correct specific risk factors in them.

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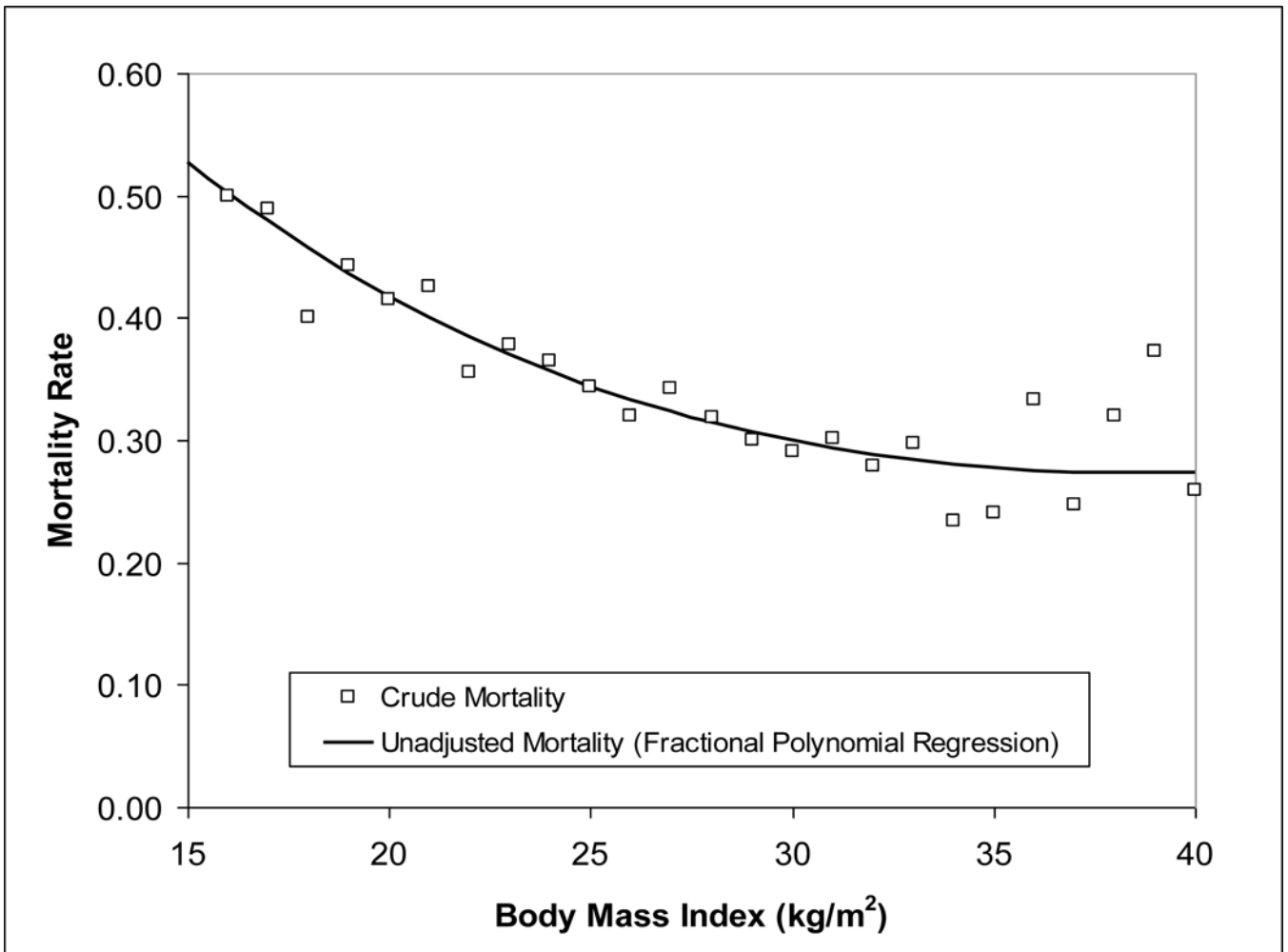


Figure 1. Obesity paradox in CHF patients: Association of body mass index (BMI) as a continuous variable and unadjusted all-cause mortality using polynomial logistic regression. Data from 7767 patients with stable CHF enrolled in the Digitalis Investigation Group trial (adapted with permission from Curtis et al. *Arch Intern Med* 2005;165:55–61²⁴)

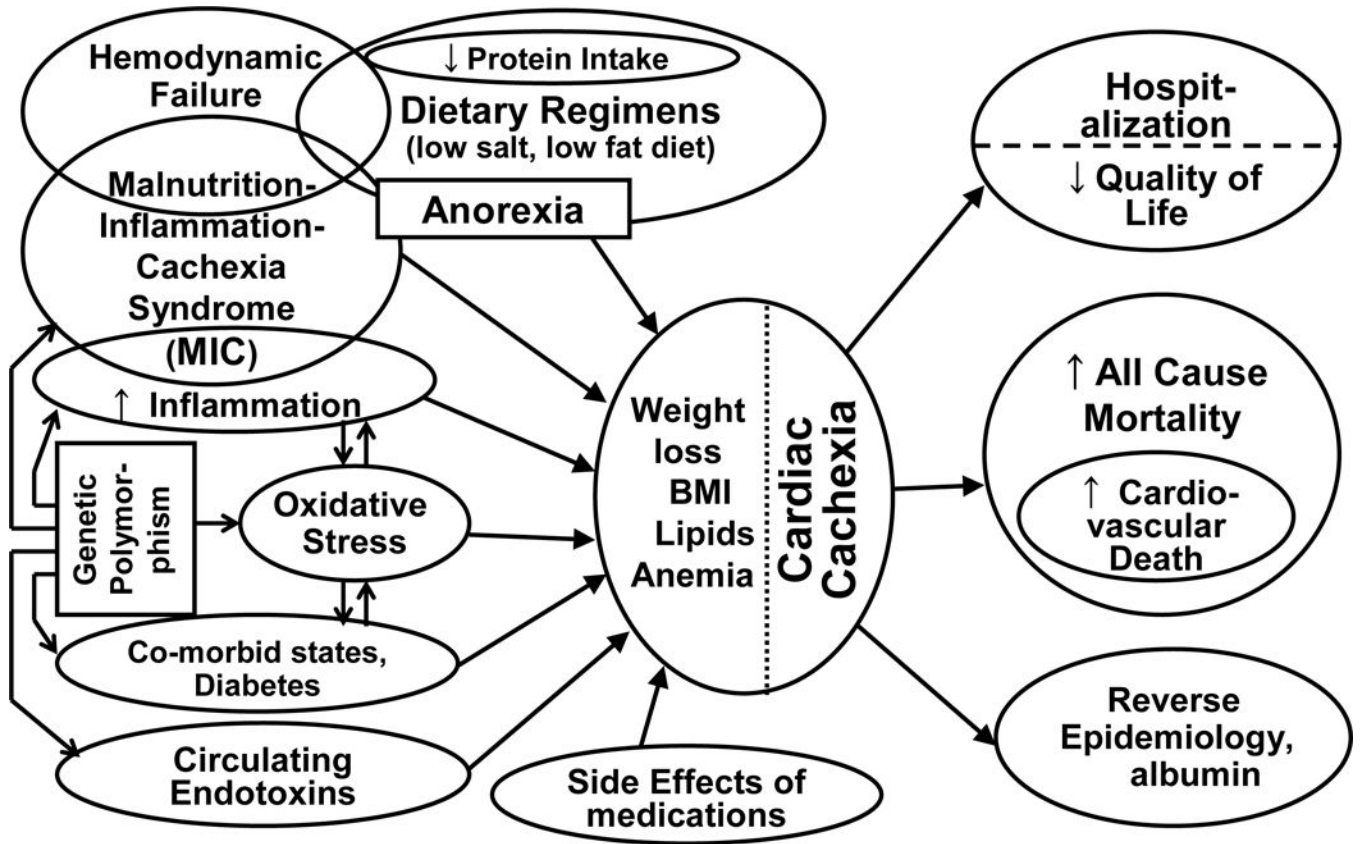


Figure 2. Schematic representation of the contributors and consequences of cardiac cachexia in CHF patients.

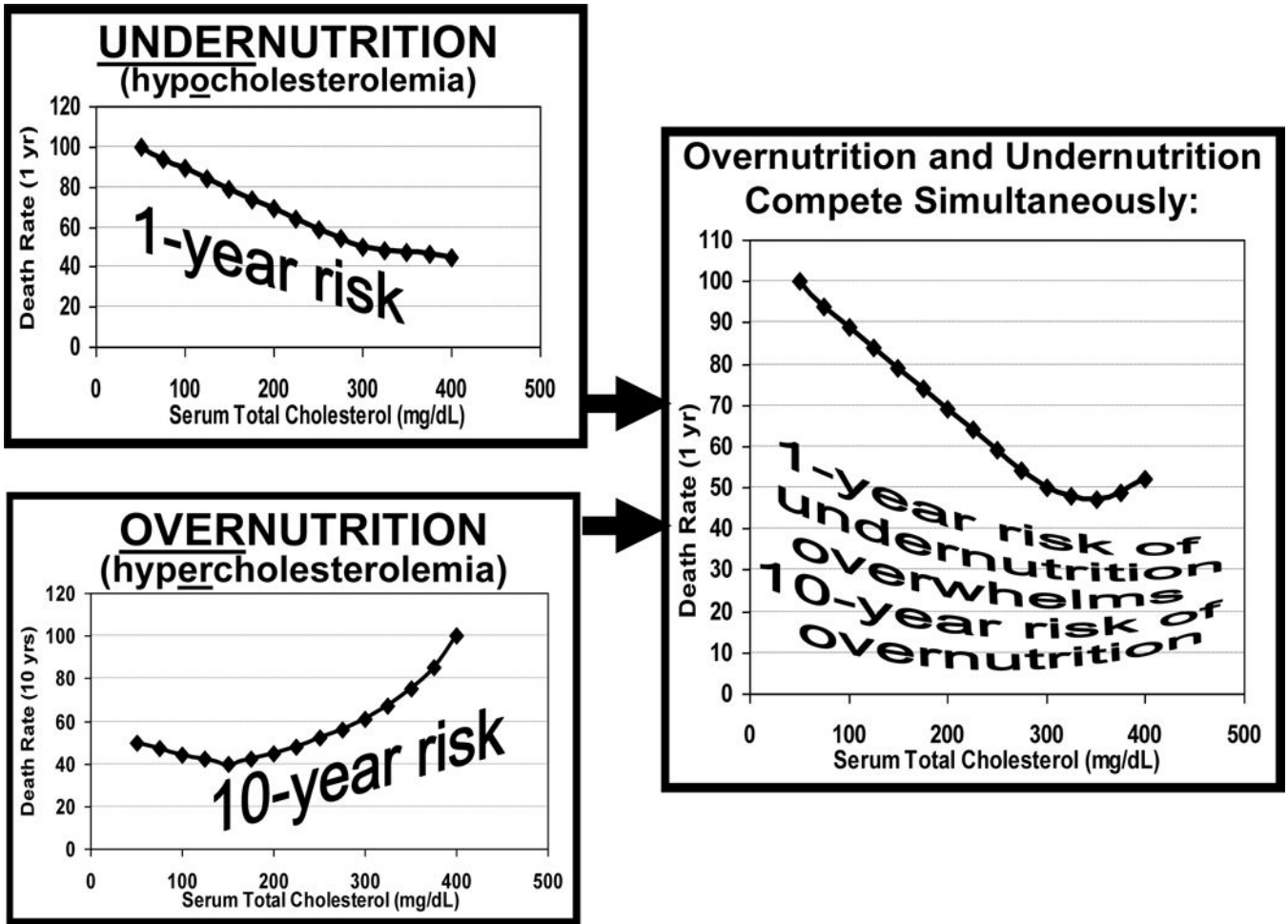


Figure 3. The Temporal Discordance Hypothesis: Competition between the short-term killer (undernutrition) and long-term killer (overnutrition) in CHF patients. (adapted with permission from Kalantar-Zadeh et al *Seminars in Nephrology* 2006;26:18–33²³⁵)

Table 1

Nutritional/anti-inflammatory interventions in CHF patients

1	Oral Interventions Oral supplements
2	Enteral Interventions Tube feeding
3	Parenteral Interventions Total parenteral nutrition
4	Hormonal Interventions Growth factors/hormones Ghrelin Melanocortin antagonists
5	Non-Hormonal Medications Anti-inflammatories (Table 2) anti-oxidants (Table 2) Appetite stimulators (Table 3) Carnitine
6	Dietary Counseling In-center/outpatient counseling

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Table 2

Anti-inflammatory & anti-oxidant agents for use in CHF patients

1	Antioxidant vitamins
	Vitamin E
	Vitamin C
	Vitamin A/carotenoid
2	Other antioxidants
3	Eicosanoids (fish oil)
4	γ-linolenic (borage oil)
5	Megestrol acetate
6	Pentoxifylline
7	Steroids/ACTH
8	NSAID
9	Anti-TNF- α agents
10	Thalidomide
11	Statins
12	ACE-inhibitors/ARB
13	beta-blockers
14	N-acetylcysteine

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Table 3

Appetite stimulants for potential use in CHF patients.

1	Anabolic steroids
2	Other corticosteroids
2	Megestrol acetate
3	Medroxyprogesterone
4	Pentoxifylline
5	Cyproheptadine
6	Dronabinol
7	Melanocortin blocker

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