HOSPITAL CHRONICLES 2014, 9(2): 1–10

SPECIAL TOPIC

The Role of Vitamin D – Iron – Thiamine in Clinical Outcomes in Patients with Heart Failure

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KEY WORDS: *heart failure; vitamin D; thiamine; iron therapy*

ABSTRACT

Several clinical and epidemiological studies have suggested a significant role of essential micronutrients in patients with heart failure, although in clinical practice the use of these agents is controversial. An overview is herein attempted of recent data regarding current knowledge on the benefits of vitamin D and B1 supplementation and iron therapy in patients with chronic heart failure.

INTRODUCTION

Congestive heart failure (HF) is a chronic medical condition with 1-3% prevalence in Western countries.[1] In spite of innovations in medical therapy, the incidence of this condition is rising, while its morbidity and mortality rates continue to remain high. Several clinical and epidemiological studies have suggested a significant role of essential micronutrients in HF patients, although in routine clinical practice the use of these agents has remained controversial for some time. However, recent trials provide evidence for certain benefits from vitamins D, B1 and iron in patients with chronic HF.

Abbreviations
ATP = adenosine triphosphate
HF = heart failure
TSAT = transferrin saturation

VITAMIN D

The metabolism of Vitamin D is complex and involves many organ systems. This is illustrated in Figure 1.

VITAMIN D SOURCES AND ACTION

In skin exposed to ultraviolet B light, the provitamin 7-dehydrocholesterol is converted to vitamin D3 (cholecarciferol). Vitamin D3 is also obtained from dietary sources. Vitamin D3 is then metabolized in the liver to 25-OH Vitamin D. Then it is often used to determine a patient's vitamin D status. 25-OH vitamin D is converted in the kidneys to its active form 1,25-OH vitamin D, and this conversion is regulated by parathyroid hormone levels, serum calcium and phosphorus levels.[2] People obtain vitamin D from sunlight exposure, dietary sources and oral supplements. Only a few foods such as salmon, eel and herring are good source of vitamin D. Luckily ultraviolet B-induced synthesis of vitamin D is extremely effective.

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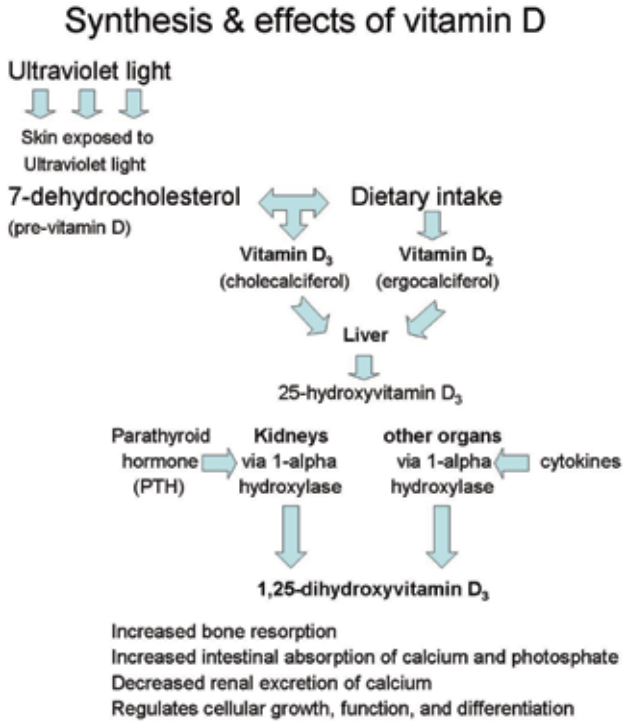

FIGURE 1. Vitamin D metabolism.

More than 200 genes, which regulate cellular proliferation, differentiation, apoptosis and angiogenesis are either directly or indirectly controlled by 1,25-OH vitamin D.[3] Vitamin D is also associated with increased insulin production,[4] decreases renin synthesis and increases myocardial contraction.

The active form of vitamin D is transported protein-bound in the blood and it is delivered in free form to cells of various target organs. Specific nuclear receptor proteins are found in many of these organs including brain, skin, skeletal muscles, cardiomyocytes,[2] vascular smooth muscles,[5] endothelium,[6] circulating monocytes and activated B and T lymphocytes.

In vitro studies demonstrate that vitamin D suppresses proinflammatory cytokines, e.g. interleukin (IL)-6, IL-2, interferon-gamma, tumor necrosis factor (TNF)-alpha) and upregulates levels of the anti-inflammatory cytokine, e.g. IL-10.[7]

EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

The different stages of vitamin D status can be classified as deficiency, insufficiency, hypovitaminosis, adequacy and toxicity. *Vitamin D deficiency* is associated with severe clinical symptoms such as rickets, osteomalacia, myopathy and calcium malabsorption. In vitamin D *insufficiency*, biochemical alterations, such as low intestinal calcium absorption and mild hyperparathyroidism, are noted without severe clinical symptoms. In addition, calcitriol levels remain normal at the expense of elevated parathyroid hormone levels.[8] In *hypovitaminosis D*, the body stores of vitamin D are already low but only minor physiological abnormalities, such as an elevated parathyroid hormone level are seen.[9] In *vitamin D adequacy* there are no perturbations in dependent bodily functions. In *vitamin D toxicity* there is intestinal calcium hyper-absorption and increased bone resorption which lead to hypercalcemia.

According with the National Health and Nutrition Examination Survey (NHANES III), low 25-OH vitamin D levels were associated with multiple health problems including coronary vascular disease, cancer, congestive heart failure, hypertension and diabetes.[10] There are data which suggest an association between low levels of 25-hydroxyvitamin-D and the accelerated development of cardiovascular disease[11-13] and its prevalence was noted to increase with increasing distance from the Ecuador because of sunlight deficiency. Recent studies also suggest that low vitamin D levels (<30 mg/ml [75 mmol/l]) are linked with the occurrence of fatal stroke,[14] sudden cardiac death,[15] valvular aortic stenosis and heart failure. Importantly, 41% of men and 53% of women[4] in the United States have levels of 25-OH Vitamin D below 28 ng/ml. In the elderly population in the United States and Europe, 40% to 100% are vitamin D deficient. It has been estimated that one billion people worldwide have vitamin D deficiency or insufficiency.[16]

VITAMIN D DEFICIENCY AND CHRONIC HEART FAILURE

Congestive HF is the end stage of hypertensive, coronary or valvular disease in many patients. There is increasing evidence to support the motion that low vitamin D status may be an important factor in the development and the pathogenesis of HF.

Recently, in the pathophysiology of HF, ideas have expanded to a more complex concept for vitamin D,[17] which seems to have indirect effect on risk factors of disease and direct effect on myocytes. Four major potential mechanisms may be important to explain the direct effects of vitamin D against the development of congestive HF.[19] These include the effect on myocardial contractile function, the regulation of inflammation cytokines, the influence on extracellular matrix remodeling and the regulation of natriuretic hormone secretion. In addition, vitamin D has a number of actions (Figure 2) that should help prevent hypertension,[20] a significant risk factor for HF.

Vitamin D suppresses the renin-angiotensin-aldosterone system and thus protects the kidneys. More than 20 years ago, several studies showed the relationship between vitamin D and cardiovascular homeostasis. Excess parathormone levels are associated with low levels of vitamin D, which may play a role in cardiovascular disease by leading to cardiomyocyte hypertrophy and interstitial fibrosis of the heart. Vitamin D suppresses cardiac hypertrophy, as it was found in animal studies and also plays a role in cardiomyocyte relaxation invalidating the hypercontractility associated with diastolic HF.

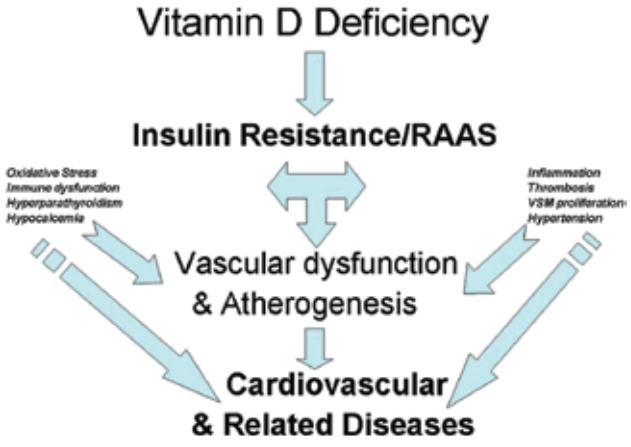

FIGURE 2. Cardiovascular consequences of vitamin D deficiency.

VITAMIN D AND HEART TRANSPLANTATION

In patients who are at end-stage HF, the question arises whether these individuals would be at high risk of vitamin D deficiency. Stein et al measured serum 25-hydroxy-vitamin D3 immediately after transplantation in heart transplant recipients. Levels were low.[21] This could be explained by malabsorption and limited exposure to sunlight. However, in order to estimate the role of low levels of vitamin D during the pre- and post- transplant period in improving survival or preventing graft rejection for recipients, further investigation is needed.

VITAMIN D SUPPLEMENTATION AND SURVIVAL IN HEART FAILURE

Vitamin D requirements vary between 60 to 200 IU per day, depending in part on age and sun exposure. Other investigators believe that optimal amounts are closer to 1000 IU daily.

Apart from an increased propensity to vitamin D deficiency in chronic HF patients, no clear data exist on improvement in clinical outcomes. Pitas et al performed a systematic review of 13 observational studies and 18 trials evaluating the effect of vitamin D supplementation on cardiometabolic outcomes.[22] The analysis revealed mixed results and the authors concluded that the association between vitamin D status and cardiometabolic outcomes was uncertain, and no significant benefit in clinical practice of supplementation was evident.

In a 20-week trial of vitamin D supplementation in patients older >70 years of age with HF and vitamin D insufficiency, a regimen of 100.000 IU of vitamin D or placebo at baseline at 0 and 10 weeks did not improve functional exercise tolerance in the 6-minute walk test. A decrease in B-type natriuretic peptide, a secondary outcome, was an intriguing observation in the treatment group, but it was counter-balanced by a decrease of quality of life. This high-quality trial contributes to the evaluation of the role of vitamin D in chronic HF. However, prospective studies are required which should focus on higher doses of vitamin D.

IRON

The importance of iron to human health is well-known and there is increasing interest in identifying the role of iron in cardiac failure. In chronic HF, treatment of anemia in patients with reduced left ventricular ejection fraction was traditionally based on erythropoietin-stimulating agents. Debate has been going on regarding whether erythropoietin is needed in addition to iron to improve exercise capacity and symptoms in anemic HF patients.

Recent studies have shown that treatment with intravenous (IV) iron can improve the quality of life in patients with chronic HF and iron deficiency, with or without anemia. In chronic HF the impairment of cardiac function affects the functional capacity of other organs such as the kidneys and skeletal muscles. The most prevalent comorbidities in chronic HF are chronic kidney disease and anemia.[23] The diagnosis and treatment of these comorbidities by physicians will most likely increase mechanisms to correct the inadequate tissue oxygen supply and impaired oxygen used by the skeletal muscles for improving exercise tolerance.[24]

Anemia in chronic HF can be the consequence of reduced glomerular filtration rate, impaired erythropoietin production and hemodilution.[25] In one study of 148 patients with anemia and HF, the majority of patients – about 57% - were found with anemia of chronic disease, due to inadequate production of erythropoietin relative to the degree of anemia and/or a defective iron supply for erythropoiesis. These findings seem to be correlated with elevated level of inflammatory cytokines.[26]

CORRECTION OF ANEMIA

In some small initial studies of correction of anemia in individuals with chronic HF and chronic kidney disease, Silverberg et al[27] achieved an increase in hemoglobin, left ventricular ejection fraction, functional class and decreases in hospitalizations for HF with erythropoietin and IV iron. In another study of anemic patients (hemoglobin ≤12 g/dl) with stable chronic HF, IV injection of iron sucrose alone over 12 days increased hemoglobin levels, decreased symptoms and improved exercise capacity.[28] However, the medical community ascribed a secondary role to the administration of oral or intravenous iron, and erythropoietin-stimulating agents received most of the attention from researchers because of its benefits.

Two recent meta-analyses of these studies with erythropoietin-stimulating agents demonstrated a beneficial effect on HF hospitalizations and some signs of symptomatic improvement but no decrease or increase in mortality. In larger studies, however, there was no significant improvement in exercise capacity despite the increase in hemoglobin.[29,30] In addition, if we take

into account the large number of patients participating in the TREAT trial (´4000), in those with HF, anemia and chronic kidney disease who received erythropoietin-stimulating agents, there was a neutral effect on mortality and non-fatal HF events. Furthermore, a higher risk of venous and arterial thromboembolic events, as well as stroke, and a trend toward hypertension were noted with the use of the erythropoietin-stimulating agent.

These findings are in contrast to the consequent clinical improvements found in recent studies in patients with HF and iron deficiency with or without anemia who received only IV iron. In the FAIR-HF trial, 459 patients were randomised to receive IV iron as ferric carboxymaltose vs placebo.[38] Among patients who received IV iron, 50% reported being much or moderately improved, as compared with 28% of patients receiving placebo, according to the patient global assessment (odds ration for improvement 2,51: 95% confidence intervals-CI, 1.75-3.61). There was also a significant improvement in the NYHA functional class. In the distance on the 6-minute walk test and quality-of-life assessments, there were no differences, and there was a trend for fewer hospitalizations and for any cardiovascular disease in the IV iron group. It is important to mention that treatment with IV iron was beneficial to both patients, with and without anemia.

In the FERRIC-HF trial the findings were also similar and consistent with the concept that impaired physical performance in iron-deficiency animal models is due to two facts: **1)** The impaired oxidative capacity of the skeletal muscle, as myoglobin, mitochondrial cytochrome and total mitochondrial oxidative capacity decreases, **2)** The diminished oxygen transport when anemia develops.[18] Finally, in the FAIR-HF trial, the outcomes assessed and the findings tended to estimate lower intensity endurance exercise correlating tightly with tissue iron deficiency.

CHRONIC HEART FAILURE AND IRON DEFICIENCY

In order to evaluate the anemia and to look further into its pathogenesis in patients with chronic HF, we must also assess vitamin B12 and folic acid levels. According with some studies, estimates of deficiency in these vitamins in individuals with chronic HF and anemia reach up to 19%. However, this seems to be of secondary importance, while iron deficiency plays a critical role in the anemia of HF and it can contribute to erythropoietin resistance, as the bone marrow will not respond to erythropoietin unless adequate iron stores are present.

An important point, according to a study by Nanas et al,[31] is that despite apparently adequate iron stores as assessed by serum iron and ferritin, up to 73% of patients with anemia, normal kidney function and advanced HF had iron deficiency as estimated by bone marrow aspiration. This study demonstrated that neither serum iron nor ferritin levels proved to be reliable markers of iron deficiency. The reason for a higher than expected serum ferritin may be due to inflammatory mediators that accompany the chronic HF syndrome and this is why in those patients a higher cut-off value of ferritin (<100 μg/lt) determines the absolute iron deficiency.

Iron is an essential trace element that can donate electrons to its ferrous form – Fe(II) – and accept electrons in its ferric-form (III). This capability makes it a useful component of cytochromes and oxygen-binding molecules, such as hemoglobin and myoglobin, but can also promote the generation of free radicals and makes iron potentially toxic.

DIAGNOSIS OF IRON DEFICIENCY

Diagnosing iron deficiency in patients with HF is very important, because iron plays a key role in oxygen uptake, transport and storage in the oxidative metabolism of the skeletal muscle and in erythropoiesis.[32] The evaluation of iron metabolism must include the determination of serum iron, transferrin, transferrin saturation (TSAT) and ferritin (Figure 3). Thus, iron deficiency may be identified when ferritin levels are <100 μg/l, accompanied by high transferrin and low TSAT; functional iron deficiency is defined as ferritin between 100 and 299 μg/l and TSAT<20% and these patients also benefit from IV iron.

Functional iron deficiency means that there is an increased uptake and retention of iron in the cells of the reticuloendothelial system, when we consider anemia of chronic disease, such as that of chronic HF. This is achieved by the expression of divalent metal transporter 1 (DMI1), which is up-regulated by cytokines. DMT1 mediates iron transport into the intestinal mucosal cells and into the activated macrophages, but the export of iron from these cells is inhibited by down-regulation of the expression of ferroportin by means of an increase in hepcidin. This protein inhibits iron absorption from the gut and hepcidin levels seem to reflect iron load and response to erythropoietin rather than inflammation and erythropoietin resistance.[34] Thus, this condition is associated with normal or increased ferritin with low serum iron, low TSAT, low transferrin and thus poor availability of iron at the bone marrow.[33]

In a recent study of 546 patients with systolic chronic HF, iron deficiency (absolute or functional) was found in 37% of patients, and iron deficiency but not anemia was related to an increased risk of death or heart transplantation in multivariable analysis reinforcing its position as an independent predictor of adverse outcome.

TREATMENT OF IRON DEFICIENCY

In patients with chronic HF and iron deficiency, IV iron therapy as demonstrated in FAIR-HF trial improves functional class and hemoglobin levels. [35] One could wonder whether oral iron, a less expensive therapy, could have a very similar therapeutic effect. The answer seems to be negative, because the absorption of oral iron preparations in the anemia of chronic disease is blocked by hepcidin.[36] Furthermore, oral

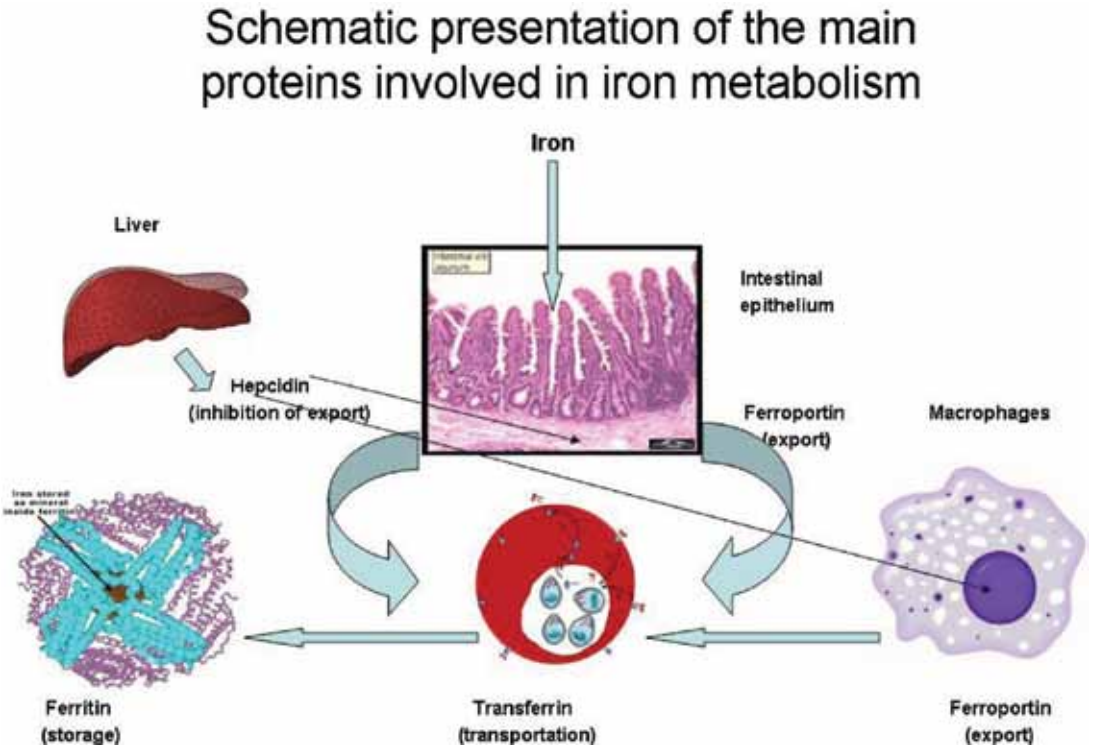

FIGURE 3. Iron metabolism.

iron administration may be poorly tolerated because of gastrointestinal side-effects and a number of drug interactions may occur, such as when co-administered with proton pump inhibitors, for example. Hepcidin also impairs iron delivery to bone marrow, which is why the anemia of chronic disease does not respond to oral iron.

CONCLUSION

Iron is a micronutrient that stands at the core of cellular metabolism and is critical for the maintenance of homeostasis. Iron deficiency constitutes a frequent co-morbidity in HF patients. Iron deficiency is gaining interest, not only as an etiological factor leading to and/or aggravating anemia in HF, but also as a therapeutic target. Only recently did clinical studies demonstrate that in patients with HF and iron deficiency, IV iron repletion was well tolerated and improved functional status, quality of life and exercise capacity.

It seems reasonable, therefore, to undertake a work-up evaluation and, if absolute or functional iron deficiency is found, to start treatment with IV iron, although further mortality and morbidity studies would help to further define the role of IV iron in HF.

Intravenous iron is provided as carbohydrate complexes with iron in its Fe(III) form and after a few hours following its administration it is taken up by the reticuloendothelial system. The majority of the dose is deposited in a long-term storage and a portion of this iron is bound to transferrin for transportation to the bone marrow. In contrast to dextran iron, currently used IV iron preparations, ferric saccharate, ferric gluconate or ferric carboxymaltose are well tolerated and have fewer hypersensitivity reactions. The total iron dose is calculated according to the Ganzoni's formula and is administered as ferric carboxymaltose in weekly doses of 200 mg as an IV bolus injection and discontinued when ferritin reaches levels >800 μg/l or when ferritin ranges at 500-800 μg/l, TSAT is >50% and hemoglobin level is >16 g/dl. Its usefulness and safety appear greater than erythropoietin-stimulating agents in patients with anemia and chronic HF. On the other hand, as in patients with thalassemia, excessive iron deposition in the heart can cause cardiomyopathy, heart failure and cardiac arrhythmias, [37] hence close monitoring of this therapy is of paramount importance.

THIAMINE (VITAMIN B1)

Vitamin B1, also called thiamine, is one of the 8 B-complex vitamins. It is named B1 because it was the first B vitamin discovered. These essential micronutrients are water-soluble, meaning that the body does not store them, and help the body to convert carbohydrates into glucose, which is used for energy generation.[39] They help the body metabolize fats and protein.

These are needed for healthy skin, hair, eyes, liver, and mainly for good brain function, and all nervous system in general.

Like other vitamins of the B complex, thiamine is sometimes called an "anti-stress" vitamin because it may strengthen the immune system and improve the body's ability to withstand stressful conditions.[40] Thiamine plays a crucial role in certain metabolic reactions and is the one that the body needs to form adenosine triphosphate (ATP) which every cell uses for energy.[40]

There are two major sources of thiamine, dietary intake and bacterial production. The greatest quantities are in several food groups, such as wheat, rice, yeast, pork, beef, poultry, fish, milk, green leafy vegetables, nuts and seeds. Conversely, bacterial production is extremely small. The quantity of reserves of the water-soluble thiamine in the lipid structures of the body cell are quite low, with the maximum storage capacity of 30 ng. The stored thiamine in the body is depleted within two weeks and clinical signs and symptoms appear in almost three months of a thiamine-deficient diet. Excess thiamine is excreted in the urine, whereas in thiamine deficiency, it is generally absent from the urine. However, a patient can be clinically thiamine-deficient despite a "normal" serum and urinary thiamine excretion level. Consequently, a fixed supply of vitamin B1 intake is required regardless of whether urinary thiamine excretion is high.

Thiamine is absorbed in the jejunum and ileum by passive as well active uptake. Then it travels to the liver and by facilitated transport enters into the red blood cells. Thiamine in serum, which is not protein-bound, is filtered at the glomerulus. Thiamine excretion takes place in the distal nephron. The factors that increase the urine flow rate would also increase thiamine excretion and may predispose individuals to thiamine deficiency.

It is a rare situation for individuals to be deficient in thiamine, although alcoholics, patients with Crohn's disease, anorexia, or patients on chronic renal dialysis may be thiamine-deficient. Depression, irritability and fatigue with abdominal discomfort are some symptoms of thiamine deficiency.[41] Individuals with thiamine deficiency may have trouble digesting carbohydrates; this allows pyruvic acid to concentrate in the bloodstream, causing shortness of breath, loss of mental alertness and cardiac dysfunction (high-cardiac output heart failure), a disease known as Beriberi.

Beriberi is the condition in which thiamine has one of the most important uses for its therapy. This illness is more common in underdeveloped countries because of malnutrition. Symptoms include shortness of breath because of pulmonary congestion, peripheral edema, tingling or burning sensation in the hands and feet, and mental confusion.[42]

The features of thiamine deficiency take one of two forms depending on whether the patient has wet or dry Beriberi. Patients with wet Beriberi have cardiovascular disturbances, which manifest as high-output or low-output cardiac failure, systemic vasodilation, lactic acidosis, edema with fluid retention. On the other hand, patients with dry Beriberi have neurological symptoms in the central and peripheral nervous systems, manifesting as Wernicke-Korsakoff disease (encephalopathy).

WERNICKE-KORSAKOFF SYNDROME

These two encephalopathies are caused by thiamine deficiency in cases of malnutrition due to alcoholism and are attributed to nerve damage in the central and peripheral nervous systems. Wernicke's encephalopathy produces confusion, ataxia, nystagmus, diplopia, and can progress to coma and death. Korsakof's syndrome or psychosis relates to memory loss, confabulation and hallucinations. Stopping alcohol can prevent additional loss of brain function and nerve damage, while thiamine therapy may improve symptoms, but does not restore memory loss.

ALZHEIMER'S DISEASE

Lack of thiamine can cause dementia in Wernicke-Korsakoff syndrome. Therefore, researchers have speculated that thiamine might help Alzheimer's disease.[43]

HEART FAILURE

Thiamine deficiency was widespread in the developing world as a result of the exclusive use of polished rice as a staple diet in many Asian countries. With the realization that polished rice could lead to thiamine deficiency, a large number of certain populations may be at high risk for developing this deficiency, including heart failure. Thiamine may be related to heart failure in other ways, such as anorexia secondary to cardiac cachexia, use of alcohol, or end-stage renal disease; more commonly, many patients with HF receive diuretics, which help rid the body of excess fluid,[44] but also increase thiamine excretion, which takes place in the distal nephron. Thus, use of high doses of diuretics in patients with HF can predispose them to thiamine deficiency. Therefore, the interest in thiamine and thiamine deficiency, particularly in the HF population, has recently re-emerged.

The aim of available therapies for HF has been firmly the prolongation of life expectancy. Although angiotensin converting enzyme inhibitors, β-blockers, aldosterone antagonists, diuretics, implantable cardiac resynchronization therapy-pacemaker/defibrillator devices, have all improved morbidity and mortality in this population, mortality rates still remain high.

For several reasons, patients with HF may have micronutrient deficiencies, one of which is thiamine deficiency.[45] Thiamine supplementation may be an adjunct therapy in order to improve the prognosis and quality of life of patients with HF.

The possible pathogenesis in the case of wet Beriberi (Table 1) is based on depletion of ATP from cardiac myocytes and the enhanced production of ATP releases in the plasma.

TABLE 1. Features of thiamine deficiency

General Features	Dry Beriberi / Wernicke-Korsakoff Sydrome	Wet Beriberi
Psychological symptoms: depression, emotional instability, mood liability, uncooperative behavior, fearfulness and agitation	**Occulomotor abnormalities:** ophthalmoplegia and optic neuropathy	High-output or low-output cardiac failure
Neurological symptoms: weakness, dizziness, insomnia, memory loss, peripheral neuropathy, pain sensitivity and sonophobia	Ataxia and gait abnormalities	Systemic vasodilatation, pulmonary and peripheral edema, and fluid retention
Musculoskeletal symptoms: backache, myalgia, and muscular atrophy	Delirium, global confusion, psychosis, and coma	Metabolic acidosis, lactic acidosis
Gastrointestinal symptoms: anorexia, nausea, vomiting and constipation	Peripheral neuropathy	Palpitations, widened pulse pressure, hypotension, bradycardia at rest, and sinus arrhythmia
	Seizures	
	Movement disorders: myoclonus and chorea	

The ATP depletion causes weakening of the cardiac muscle function, finally leading to HF.[46] Myocytes fail to produce ATP and so adenosine monophosphate is accumulated and converted to adenosine. The increased production of intracellular adenosine provokes its build-up in the cells, eventually causing its release into the plasma. Adenosine in the plasma denotes as systemic vasodilation, flushing and headache. The derangement of reactions causes a blockade in the citric acid cycle thus preventing the conversion of pyruvate to acetyl-CoA and ultimately ATP formation, causing cellular acidosis and increasing intracellular free fatty acid levels. The absence of ATP causes the body to upregulate glucolysis and use fat resources to accomplish its energy requirements. These fat resources proceed to not only provide energy but also produce ketones, which can be used for production of acetylo-CoA for extra hepatic tissues.

In chronic thiamine deficiency the body fat resources ultimately run out if other sources of acetyl-CoA such as ethanol are not being used. Therefore, stopping alcohol ingestion in patients with thiamine deficiency may actually result in rapid death of the patient.[47] The pyruvate accumulation, from increased production caused by enhanced glycolysis and decreased utilization, because of its conversion to acetyl-CoA results in its alteration to lactate. The increased production of lactate ends up to lactic acidosis. This process severely disturbs the mechanisms of the normal cardiovascular system. The ventricular filling pressures are increased with increased oxygen consumption. The resistant vessel is damaged, which causes decreased peripheral vascular resistances leading to arteriovenous shunting of blood, increased cardiac output and venous congestion. Additionally, these patients can have signs and symptoms of increased catecholamine levels, low diastolic pressure and a widened pulse pressure resulting from the severe cardiovascular disturbances.

RISK FACTORS FOR THIAMINE DEFICIENCY

As already alluded to, thiamine deficiency in patients with congestive HF is multifactorial.[48] It may be present in these patients as a result of reasons irrelevant to HF, such inadequate dietary intake, advancing age, trauma, surgery, fever, malabsorption syndromes, severe infections, eating disorders, cancer, alcohol excess, inborn errors of metabolism, gastrointestinal surgery, persistent diarrhea, acquired immunodeficiency syndromes or drug therapy such as use of diuretics. Medications, such as phenyntoin, penicillins, cephalosporins, aminoglycodides, tetracycline derivatives, fluoroquinolones, sulphonamide derivatives, all may cause thiamine deficiency. Patients with HF experience early satiety and cachexia[49] both of which may be responsible for low dietary thiamine intake. In addition, the use of diuretics in combination with advanced age may be responsible for low levels of thiamine.[50] The increase in venous pressure that is usual in chronic HF increases lymphatic production causing lymphatic obstruction, which impairs absorption from intestines and thus accelerates thiamine deficiency. In summary, the principal factors associated with thiamine deficiency in patients with HF are use of diuretics, malnutrition, preserved renal function, severe HF and advanced age (Table 2).

Thiamine has multiple effects on the cardiovascular system. It has important hemodynamic effects on the circulatory system and direct positive effects on the heart. Low levels of thiamine contribute to the higher than normal basal metabolic rate in patients with HF.[51] Thiamine deficiency is associated with depressed cardiac contractility, dysrhythmias and cardiac

TABLE 2. Risk factors for thiamine deficiency

Diet Related	Comorbid Conditions	Others
Inadequate dietary intake, excess alcohol ingestion, malabsorption syndromes, eating disorders, and drugs such as diuretics, phenytoin, penicillins, cephalosporins, aminoglycosides, tetracycline derivatives, fluoroquinolones, sulfonamide derivatives, and trimethoprim	Heart failure, severe infections, trauma, surgery, cancer, acquired immunodeficiency syndrome, inborn errors of metabolism, gastrointestinal surgery, fever, and persistent diarrhea or vomiting	Advancing age, institutionalization, and frequent hospitalization

hypertrophy. Several clinical trials have shown that thiamine supplementation increases the systolic, diastolic and central venous pressures, with an increase of left ventricular ejection fraction and a reduction of heart rate.[52] Thiamine acts as a vasodilator and decreases the afterload, thus improving cardiac function. It has also suggested that thiamine may increase diuresis and natriuresis in patients with HF receiving diuretics, a beneficial effect for these individuals.

DOSAGE FOR THIAMINE SUPPLEMENTATION

The recommended dosages of thiamine vary according to the case of proven deficiency. For example, the daily allowance is 1.1-1.2 mg/d orally but in patients at risk, thiamine should be given up to 200 mg three times a day (Table 3).

A rapid improvement of patient is generally noted after thiamine supplementation, as a result of sudden closure of arteriovenous shunts causing volume overload. As previously mentioned, thiamine deficiency can lead to de novo HF and adversely affect pre-existing cardiac dysfunction. Therefore, the prevalence of thiamine deficiency represents a dangerous clinical status in HF patients, which varies with the individual conditions of each population, their nutritional status, drug use and the presence of comorbid situation.

Thiamine deficiency is estimated to range from 21% to 98% in patients with HF and its prevalence is higher in those with advanced age, taking diuretics, more severe failure, multiple diseases and varies in different studies (Table 4). The use of diuretics leads to thiamine deficiency because the excretion of thiamine in urine is directly proportional to urine flow. For that reason any increase of urine flow as occurs with use of diuretics may lead to an enhanced excretion of thiamine.

Furosemide has also been shown to reduce the uptake of thiamine by the cardiac myocytes.[53] In addition, furosemide contributes to the development of thiamine deficiency because of its effects including anorexia, decreased intestinal thiamine

TABLE 4. Prevalence of thiamine deficiency in heart failure

Study	Prevalence
Wooley et al	21-98% in patients with heart failure
Sica	3-96% in patients with heart failure
Allard et al	13-93% in patients with heart failure
Lee et al	13-33% in patients with heart failure
Brady et al	21% in patients with heart failure
Levy et al	0% in younger patients with stable heart failure
Seligmann et al	91% in patients with heart failure and taking diuretics

TABLE 3. Dosage for thiamine supplementation

Recommended Daily Allowance	1.1-1.2 mg/d Orally
Risk of thiamine deficiency	100 mg 3 times daily until thiamine levels normalize
Proven thiamine deficiency	200 mg 3 times daily until thiamine levels normalize
Alcoholics without encephalopathy	50 mg/d orally
Patients on a refined grain diet	5-15 mg/d orally
Mild neuropathy	20-30 mg/d orally for 2 weeks
Severe neuropathy	20-30 mg/d orally for several weeks
Wet Beriberi	100 mg/d intravenous for several weeks
Prophylactic dose in HF	10-20 mg/d orally

absorption and cellular hyponatremia or hypomagnesemia.[54] More specifically, patients with chronic HF who are taking furosemide >80 mg/d or bumetanide >2 mg/d for prolonged duration (>6 months) are at an especially increased risk for developing thiamine deficiency.[55] Thus, patients with HF may be at risk for developing certain mirconutrient deficiencies including thiamine deficiency,[56] and may benefit from thiamine supplementation, especially those at advanced stages. A recent meta-analysis of randomised double-blind, placebo-controlled trials has indicated that thiamine supplementation results in a significant improvement in net change of left ventricular ejection fraction (3.28%; 95% CI 0.64% - 5.98%) in patients with systolic HF.[57]

While more research is needed to fully elucidate the clinical impact of thiamine deficiency in chronic HF patients, recent evidence has indicated that supplementing with thiamine has the potential to improve left ventricular ejection fraction and in general to improve cardiac function, urine output, weight loss, signs and symptoms of HF. Therefore, this simple therapy should be tested in large scale randomized clinical trials to further determine the effect of thiamine in HF.

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