Chronic Heart Failure and Micronutrients

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Heart failure (HF) is associated with weight loss, and cachexia is a well-recognized complication. Patients have an increased risk of osteoporosis and lose muscle bulk early in the course of the disease. Basal metabolic rate is increased in HF, but general malnutrition may play a part in the development of cachexia, particularly in an elderly population. There is evidence for a possible role for micronutrient deficiency in HF. Selective deficiency of selenium, calcium and thiamine can directly lead to the HF syndrome. Other nutrients, particularly vitamins C and E and beta-carotene, are antioxidants and may have a protective effect on the vasculature. Vitamins B_6, B_{12} and folate all tend to reduce levels of homocysteine, which is associated with increased oxidative stress. Carnitine, co-enzyme Q_{10} and creatine supplementation have resulted in improved exercise capacity in patients with HF in some studies. In this article, we review the relation between micronutrients and HF. Chronic HF is characterized by high mortality and morbidity, and research effort has centered on pharmacological management, with the successful introduction of angiotensin-converting enzyme inhibitors and beta-adrenergic antagonists into routine practice. There is sufficient evidence to support a large-scale trial of dietary micronutrient supplementation in HF. (J Am Coll Cardiol 2001;37:1765–74) © 2001 by the American College of Cardiology

Heart failure (HF) affects approximately 10% of those over 80 years old (1). It is the leading cause of death in industrialized countries (2) and the single most common reason for medical admissions to hospitals (3). Recent therapeutic advances have led to benefits with regard to symptoms and prognosis (4). Nevertheless, a poor prognosis, persistently high readmission rates (5) and reduced quality of life (6) remain features of the condition.

Much research effort has been expended on drug treatments for chronic heart failure (CHF), but there has been little attention paid to nonpharmacological management. While it is generally considered that a high sodium diet may be detrimental, little is known about other aspects of diet in HF in terms of both general nutrition and micronutrients such as vitamins and minerals. In this article, we will review what is known about nutrition in HF, particularly as it relates to micronutrients, and consider the potential therapeutic implications.

METHODS

A search strategy using Medline was used to identify all articles published containing the key words "heart failure" and its cognates and each of the micronutrients under discussion. For this purpose, we defined a "micronutrient" as an essential dietary component present in trace amount. For each micronutrient, we considered the evidence from animal experiments and the evidence that the nutrient may be relevant to HF in man.

GENERAL NUTRITION

Cardiac cachexia was described by Hippocrates: "The flesh is consumed and becomes water . . . the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest and thigh melt away" (7). Weight loss or frank cachexia is commonly seen (8), the prevalence increasing with worsening symptoms (9,10). Cachexia worsens the already poor prognosis by a factor of 2.6 (9). More subtle loss of muscle bulk occurs early in the disease (11).

There may be multiple etiologies to the weight loss (12). Heart failure makes patients less active (13), which may result in loss of muscle bulk, but the disease process itself seems to contribute to the loss (14). Some HF patients (15,16), but not all (17), have an increased resting metabolic rate of up to 70% of daily energy expenditure, and this proportion increases with symptomatic class (18).

There is a shift toward catabolism in HF (19). Catabolic steroids are elevated (20), and there is an increase in catabolic relative to anabolic steroids (21,22). There is also insulin resistance (23,24) and resistance to the effects of growth hormone (25). Tumor necrosis factor-alpha is raised in HF (26), particularly in those with weight loss (21,27). It may stimulate loss of appetite through downregulation of the $alpha_3$-adrenoceptors (28) and by the induction of leptin expression in adipose tissue and reduction in body fat stores (29).

Previous dietary studies in HF have been inconclusive but have failed to take into account nutrient or caloric intake (30) or have involved small numbers of patients (31). Gastrointestinal malabsorption (possibly as a consequence of gut edema) may be a cause of impaired nutrition. Fat malabsorption particularly may affect elderly patients with cardiac cachexia (32), which may, in turn, affect absorption of fat-soluble vitamins.

Abbreviations and Acronyms

AMI = acute myocardial infarction
CHF = chronic heart failure
HF = heart failure
LV = left ventricular

MINERALS

Deficiencies of specific micronutrients can cause HF. Patients with HF from other causes have a number of risk factors for micronutrient deficiency. They are usually elderly, may have a poor general diet (33) and are prone to excess urinary losses due to diuretic therapy.

Calcium and vitamin D. Calcium absorption is reduced in people over 70 years of age because the gut may be less sensitive to calcitriol and also because of lower renal synthesis of calcitriol. Loop diuretics are calciuric (but thiazides are not) (34). Older people make less vitamin D in the skin after exposure to ultraviolet light (35).

There is a link between low calcium intake and higher mortality from ischemic heart disease in postmenopausal women (36). Hypocalcemia-induced cardiomyopathy in humans, usually in young children with a congenital cause for hypocalcemia, can respond dramatically to calcium supplementation (37–39). Low calcium levels are potentially proarrhythmic, being associated with QT prolongation (40) and torsades de pointes (41), and hypocalcemic-associated ventricular fibrillation has been reported (42).

Osteopenia or osteoporosis is seen in half the patients with severe HF (43). Heart failure patients with cachexia have lower calcium levels and lower bone mineral density (44) than noncachectic patients and normal subjects.

Vitamin D is also important in the functioning of the cardiovascular system. Rats fed on vitamin D-deficient diets, but with calcium levels maintained by high-dose calcium supplements, develop deteriorating myocardial contraction. Myocardial contraction returns to normal only when vitamin D is supplemented (45). In another rat model, vitamin D and retinoic acid reduced the hypertrophic process induced by endothelin (46), which is raised in HF (47).

Magnesium. Loop and thiazide diuretics increase magnesium loss. The incidence of magnesium deficiency in CHF has been reported at more than 30% and is accompanied by muscular magnesium deficiency (48), which may contribute to symptoms of fatigue. Magnesium deficiency also causes a positive sodium balance and negative potassium balance (49).

Hypomagnesemia is associated with a worse prognosis in HF (50,51) and an increase in the rate of ventricular ectopic beats (50,51), both in the presence of left ventricular (LV) dysfunction and normal cardiac function (52), and, in rats, magnesium deficiency can increase the rate of adrenaline-induced ventricular tachycardia (53). Magnesium replace-

ment results in a fall in the rate of ventricular arrhythmias (54,55).

Deficiency of magnesium can lead to cardiac failure in rats (56). This can be inhibited by sufficient quantities of ascorbate (vitamin C), suggesting that free radical production may be involved (57). Indeed the magnesium-dependent isoform of adenylyl cyclase, an antioxidant enzyme, is reduced in rats with CHF (58). Heart failure as a consequence of hypomagnesemia has also been observed in humans, and correction of the magnesium levels leads to improvement in (LV) function (59). Low magnesium status is common in elderly patients with atrial fibrillation and HF and can precipitate digoxin toxicity (60,61). Ventricular arrhythmias in the context of idiopathic cardiomyopathy may respond to magnesium therapy (62).

Zinc. Zinc deficiency is common in the elderly (63). Low zinc levels correlate with intake of cardiovascular medication and also with reduced nutritional protein (63). Low serum (64,65) and high urinary zinc levels are found in HF (66), possibly as a result of diuretic use.

Zinc deficiency is associated with higher levels of lipid peroxides in rat hearts (67). Levels of lipid peroxidation are markers of oxidative stress, suggesting that zinc acts as an antioxidant (68). The combination of zinc deficiency and ethanol can lead to contractile dysfunction in pre-ischemic conditions in the rat model (69).

Manganese. Manganese is a constituent of the antioxidant enzymes superoxide dismutase and adenylyl cyclase. Levels of manganese are elevated in HF (64), and the expression of the manganese isoform of adenylyl cyclase is not reduced in rats with chronic LV dysfunction in contrast with the magnesium-dependent isoform (58). However, mice lacking the gene for manganese-superoxide dismutase die at 10 days of a dilated cardiomyopathy (70). Adriamycin—a well-known cause of dilated cardiomyopathy—is associated with lower myocardial levels of manganese-superoxide dismutase (but not copper or zinc superoxide dismutase) and glutathione peroxidase in rats (71).

Copper. Copper plays a role in the regulation of oxidative free radicals, and deficiency increases the susceptibility of lipoprotein peroxidation (72). Copper restriction leads to an increased risk of myocyte oxidative damage (73) and may lead to an increase in plasma cholesterol concentrations (74,75).

Long-term copper restriction in rats can lead to myofibrillar disarray and mitochondrial fragmentation (76). Cytochrome C oxidase activity is decreased in copper deficiency (77), which could lead to mitochondrial impairment and contribute to cardiac dysfunction. Copper-deficient cardiomyopathy is a recognized entity (78), and the identification of the genetic basis for defects in the copper-dependent ATP-ases have indicated a possible role of copper deficiency in experimental and human cardiomyopathy (79).

Selenium. Selenium is a constituent of the antioxidant enzyme glutathione peroxidase. Pure selenium deficiency is

rare, but deficiency symptoms may occur when there is an additional stress such as a vitamin E deficiency. An endemic cardiomyopathy in China, Keshan disease, is a consequence of selenium deficiency, which is also a risk factor for peripartum cardiomyopathy (80). Selenium-deficient cardiomyopathy has also been described in Western countries, for example, in patients on long-term total parenteral nutrition (81).

Ischemic heart disease and peripheral vascular disease have been linked to low selenium levels (82). Selenium deficiency leads to increased levels of lipid peroxidation and, thereby, an increase in oxidative stress. Selenium may protect tissues from oxidative damage, preserve cells' ability to produce ubiquinone and also reduce its breakdown by oxidative degeneration (83). Deficiency leads to mitochondrial ultrastructural changes such as loss of cristae (84).

In pig models of myocardial infarction, selenium reduced the occurrence of late ventricular potentials in the border zone (82). A selenium-based antihypertensive agent (85), which may work by the smooth muscle relaxant properties of the metal, is under development.

VITAMINS

Vitamin A. There is epidemiological evidence associating low beta-carotene intake and the risk of acute myocardial infarction (AMI) (86). It has, in combination with vitamin E and selenium, been shown to reduce overall cardiovascular mortality in a low-risk population (87), but, alone, it may reduce cardiac events (88). There is little clear evidence supporting its routine supplementation in patients with HF (89), and there are no published data on levels in CHF.

Thiamine (B_1). Thiamine (B_1) is a coenzyme for decarboxylation in carbohydrate metabolism. Deficiency leads to impaired oxidative metabolism through inhibition of the citric acid cycle and the hexose monophosphate shunt. Thiamine deficiency can induce high-output cardiac failure due to the accumulation of pyruvate and lactate, leading to intense vasodilation. Response to thiamine is brisk and often with full recovery.

In rats, myocyte contraction is reduced during thiamine deficiency (90). Frusemide-induced thiamine deficiency was first described in rats (91), and thiamine uptake by cardiac myocytes is significantly impaired both by digoxin and frusemide, the drugs having an additive effect if given together (92). Low whole blood thiamine levels have been documented in patients with CHF on loop diuretics (93,94) and hospitalized elderly patients (95,96).

Thiamine supplementation in patients with moderate-to-severe CHF taking 80 mg of frusemide induced a significant improvement in LV ejection fraction and symptoms (97) and a rise in blood pressure of 10 mm Hg (93).

Riboflavin (B_2). Rats fed on a riboflavin-deficient diet have abnormal lipid metabolism, with a reduction in the beta-oxidation of fatty acids. It is not known whether riboflavin deficiency has any detrimental effect on cardiac

functioning. Children with CHF due to congenital heart disease have an increased risk of riboflavin deficiency (98).

Niacin and pantothenic acid. There is no evidence connecting these nutrients to heart disease.

Vitamin B_6. Low pyridoxal-5′-phosphate is a risk factor for coronary artery disease and extracranial carotid artery disease mediated, in part, by elevated homocysteine levels (99–101). However, low B_6 levels are an independent risk factor for coronary artery disease even when homocysteine is taken into account (102). There are no reports of pyridoxal-5′-phosphate levels in HF.

Folate. Folate is required for the conversion of homocysteine to methionine, and a strong inverse relationship exists between folate consumption and homocysteine levels among patients with and without hyperhomocysteinemia (103,104).

Tissue levels of vitamins B_{12}, B_6 and folate are not closely related to blood levels, and many more elderly patients may be deficient than are recognized (105). There is epidemiological evidence of an inverse link between folate consumption and risk of coronary heart disease (106,107).

Vitamin B_{12}. Vitamin B_{12} deficiency is associated with elevated homocysteine and, thereby, an elevated risk for coronary artery disease (99,100), but no published work has looked at B_{12} status in patients with heart disease.

Vitamin C. A 20-year follow-up study suggested that higher levels of intake of vitamin C correlated closely with a reduced risk of death from stroke, and this association was as strongly related with death as diastolic blood pressure (108). There was however, no relation between vitamin C intake and deaths from heart disease, a finding replicated elsewhere (109). In contrast, a study from Finland on middle-aged men showed an increased risk of death from coronary heart disease over eight years of follow-up in those with low plasma ascorbate concentration (110).

The oxidation of low-density lipoprotein has been proposed to be one of the initiating features in the process of atherosclerosis. In a hamster model, pretreatment with vitamin C before oxidized low-density lipoprotein exposure prevented leukocyte adhesion to the endothelium as well as the formation of leukocyte-platelet aggregates (111).

Hypertensive patients have an attenuated vasodilatory response to acetylcholine, which is partially reversed by vitamin C (112), and ascorbic acid supplementation can significantly lower blood pressure in hypertensive patients (113). Vitamin C improves endothelial function in diabetics (114,115) and smokers (116) when infused intra-arterially (cigarette smokers have lower plasma and leukocyte levels of vitamin C [117]). Hypercholesterolemic endothelial dysfunction (118) (possibly due to oxidative stress) is improved by vitamin C infusions (119). Thirty days of oral treatment with vitamin C improves endothelium-dependent vasodilation in patients with coronary artery disease (120), and even a single dose of 2 g can improve vasomotor function after 2 h (121).

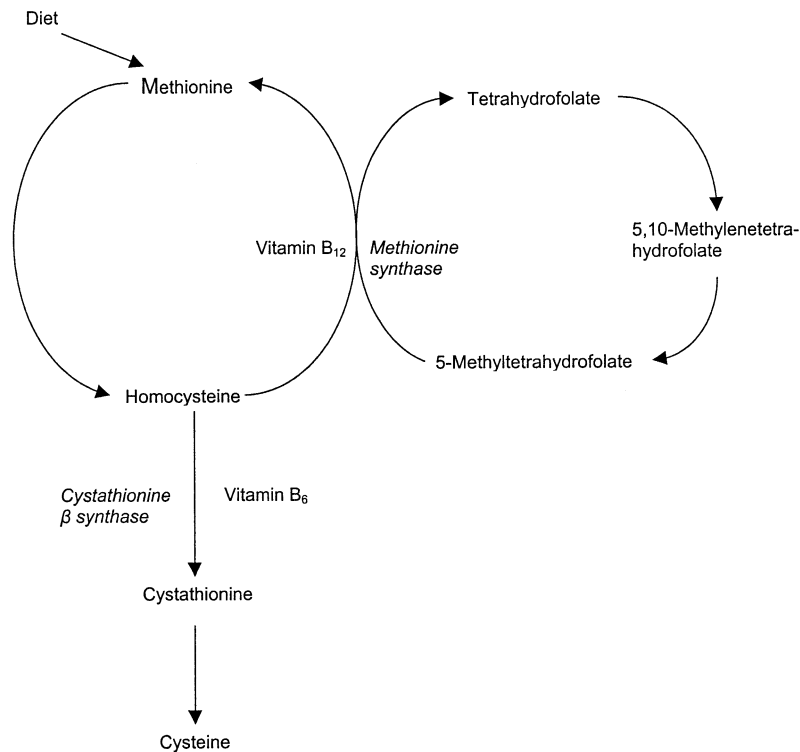Whether vitamin C levels are reduced in HF is unknown,

Figure 1. Homocysteine metabolism. Homocysteine metabolism is dependent upon folate and vitamins B_6 and B_{12}, and deficiencies of any of these may result in an increase in homocysteine.

but there is evidence that the elderly are deficient (33). Improvements of endothelial dysfunction in HF have been seen with vitamin C (122).

Vitamin E. High vitamin E intake is associated with a lower incidence of coronary heart disease in middle-aged subjects (123). The men in the top 20% of vitamin intake had a 40% lower risk of developing coronary artery disease (124), and, in women, a 34% risk reduction was seen (125). Similar results are seen in those 65 years old and older with additional benefits if subjects took both vitamin E and vitamin C supplements (126).

Vitamin E in healthy volunteers led to a reduction of platelet stickiness (127,128), an effect that has also been seen in diabetics and heart transplant recipients (129,130). Vitamin E inhibits platelet protein kinase C stimulation at physiological concentrations (131,132), which gives alpha-tocopherol the ability to control smooth muscle cell proliferation (133). In healthy adults, pretreatment with 800 IU of vitamin E and 1 g of vitamin C leads to normalization of the responsiveness of the vascular endothelium after a high-fat meal (134), and the endothelial function of cholesterol-fed rabbits improves with low-dose alpha-tocopherol (135).

Vitamin E leads to reduced surface expression of adhesion molecules on leukocytes and endothelial cells (136), resulting in reduced leukocyte-endothelium cell interactions.

In a pig model of acute infarction, high dose vitamin E combined with intravenous vitamin C, led to significantly less myocardial damage (137). This finding suggests that vitamin C aids the antioxidant action of vitamin E, and it may be able to regenerate formed vitamin E radicals at the border of the lipid and aqueous phase in cell membranes (138).

Despite these theoretical reasons for benefit from vitamin E, there are few clear data to suggest that it benefits patients with ischemic heart disease (139,140). Vitamin E reduces indexes of oxidative stress in HF patients (141). The use of vitamin E after AMI has been advocated by some, but it is far from being established therapy (142,143). The Heart Outcomes Prevention Evaluation (HOPE) study did not show any benefit for vitamin E treated patients at high risk of coronary disease (144), and a large multicenter postinfarction trial also showed no benefit from using vitamin E (145).

Ubiquinone (co-enzyme Q_{10}). Co-enzyme Q_{10} is an endogenous vitamin-like, fat-soluble quinone found in high concentrations in the mitochondria of myocardium, liver and kidney. It is an electron carrier in the mitochondrial synthesis of ATP, has membrane stabilizing properties and is a powerful antioxidant.

Patients with HF have lower levels of myocardial coenzyme Q_{10} compared with controls (146,147). Low plasma coenzyme Q_{10} levels are associated with an increased mortality in HF (148), but there is disagreement on the benefits of ubiquinone in patients with CHF. Uncontrolled studies have shown beneficial effects on ejection fraction, exercise tolerance and New York Heart Association status at

Table 1. The Potential Contribution of Micronutrient Deficiency to the Heart Failure Syndrome

Micronutrient	Deficiency State	Relevance of Deficiency to HF	Effects of Supplementation
Thiamine	Beri beri	Specific cardiomyopathy and frusemide-induced thiamine deficiency (93)	Improvements in hemodynamics (93,97)
Riboflavin		Increased prevalence in children with chronic heart failure (98)	None
Magnesium	Arrhythmias	Arrythmogenic (51); can worsen heart failure (56,59)	Reduced arrhythmias (54), improvement in cardiac function with replacement (59)
Calcium/vitamin D	Osteoporosis	Osteoporosis common (43); hypocalemia-induced cardiomyopathy (38)	Improvements in cardiomyopathy (38), reduced effects of endothelin
Zinc		Common in those with heart failure (66); contractile dysfunction in combination with ethanol (69)	Not known
Copper		Myocyte damage (73), myofibrillar disarray (76), copper deficient cardiomyopathy (78)	Not known
Selenium		Selenium deficient cardiomyopathy (81)	Not known
Vitamin A		Loss of antioxidant properties	Not known
Niacin	Pellagra	Unknown	Not known
Vitamin B_6		Elevation of homocysteine levels (102)	Not known
Pantothenic acid (vitamin B_5)	None		Not known
Folate	Macrocytic anemia	Common in the elderly (105); homocysteine levels raised (103)	Not known
Vitamin B_{12}	Pernicious anemia	Homocysteine levels raised	Not known
Vitamin C	Scurvy	Loss of antioxidant	Improves endothelial function (114–116,119), acts as antioxidant (111)
Vitamin E		Reduced platelet aggregation (128); inhibition of smooth muscle proliferation (132)	Reduced oxidative stress in HF (141)
Ubiquinone		Low in heart failure patients (146); associated with increased mortality (148)	Improved ejection fraction, exercise tolerance, symptoms (149–151)

The final column summarizes the evidence in favor of dietary supplementation in HF.
  HF = heart failure.

a variety of doses (149–151). Some placebo-controlled trials (152,153) have given similar results and also show a reduction in hospitalizations (153), but other randomized controlled trials have shown no benefit from coenzyme Q_{10} therapy (154–156).

The production of ubiqinone is reduced by hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy (157,158). There is overwhelming evidence of the benefit of statins for the secondary prevention of coronary heart disease, but patients with HF have been specifically excluded from statin trials. It may be that the effect of reducing ubiquinone in such patients is deleterious.

HOMOCYSTEINE AND HEART DISEASE

Several of the vitamins described interact through the metabolism of homocysteine (Fig. 1). Hyperhomocysteinemia is a potent risk factor for cardiovascular disease (159,160). Levels of only 12% above the upper limit of normal are associated with a threefold increase in risk of AMI (160). Levels rise with age, which may be a reflection of particularly poor intake of vitamins B_{12} and B_6 and folate in the elderly population (161). Homocysteine is also important independently of these vitamins (162).

A hyperhomocysteinemic state could promote atherosclerosis by:

1) alteration of platelet function and coagulation factors (163–165),
2) endothelial damage and dysfunction (166,167),
3) encouraging the oxidation of low-density lipoprotein (168,169),
4) smooth muscle proliferation (170,171), and
5) endothelial-leukocyte interactions (172).

Homocysteine-lowering treatment with folic acid and vitamin B_6 is possible (173), and, in the siblings of patients with premature atherosclerotic disease, this therapy is associated with a decreased occurrence of abnormal exercise tests (174).

OTHER NUTRITIONAL SUPPLEMENTS

Carnitine. Carnitine supplementation is thought to improve the utilization of pyruvate in the Kreb's cycle (175) and, thereby, improve muscle metabolism. It has been investigated in patients undergoing cardiac surgery (176) and in patients with angina pectoris (177–179), AMI (180,181), shock (182) and peripheral vascular disease (183). There was some improvement on exercise tolerance in patients with limiting ischemic symptoms, but there remains a lack of strong evidence for the use of carnitine in any of these situations. Oral propionyl-L-carnitine has, in some studies (175) but not all (184), shown improved

exercise tolerance (but not hemodynamic variables) in patients with CHF.

Creatine phosphate. Creatine is used to improve athletic performance. Patients with CHF develop a skeletal myopathy (185). Muscle contraction and relaxation is fuelled through the dephosphorylation of ATP, which must be rapidly resynthesized. Creatine serves as a phosphate donor to maintain high levels of intracellular ATP, and creatine supplementation increases the rate of phosphocreatine resynthesis (186). Skeletal muscle strength and endurance are improved in patients with CHF after short-term oral creatine supplementation, but there is no effect on cardiac contractility (187). Creatine administered intravenously improves ejection fraction (188). The improvements in skeletal muscle function are predominantly seen in patients with low levels of creatine and phosphocreatine in their skeletal muscles (187), and this is not a ubiquitous finding in patients with CHF (187,189).

It is possible that creatine is of benefit in some CHF patients, but long-term safety issues have yet to be addressed; the improvements have not been shown to be sustained, and the patient group most likely to benefit can currently be identified only by muscle biopsy.

SUMMARY

Deficiency of many micronutrients and vitamins is associated with the development of HF or may contribute to cardiovascular disease (Table 1). Patients with CHF may become deficient in micronutrients due to reduced intake, excessive consumption in some instances and increased loss induced by diuretic therapy. In addition, HF is associated with general loss of body tissue. It is possible that modern treatment of HF and an improved quality of life reduces the incidence of nutritional deficiency. The effects of protein-energy dietary support in HF are not known. Studies of supplementation of some individual micronutrients have shown improved exercise tolerance and reduced symptoms.

Micronutrient supplementation is a potentially simple treatment, and the effects need to be tested in a randomized, placebo-controlled trial in patients already receiving optimal medical therapy. Two alternative approaches are to conduct a single trial with multiple nutrients or multiple trials looking at each nutrient in turn. The former strategy would at least give an answer over a relatively short period, and further investigation could be aimed at identifying a particular factor if the trial was positive.

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