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The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure

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Aims Chronic heart failure (CHF) is a common and leading cause of death in industrialized countries. The potential benefits of micronutrient supplementation in CHF are extensive. Therefore, we examined the influence of long-term multiple micronutrient supplementation on left ventricular (LV) function, levels of pro-inflammatory cytokines, and quality-of-life (QoL) in elderly patients with CHF.
Methods and results Thirty CHF patients [age 75.4 (0.7), mean (SEM), LV ejection fraction (LVEF) $\leq$35%] were randomized to receive capsules containing a combination of high-dose micronutrients (calcium, magnesium, zinc, copper, selenium, vitamin A, thiamine, riboflavin, vitamin B_6, folate, vitamin B_{12}, vitamin C, vitamin E, vitamin D, and Coenzyme Q10) or placebo for 9 months in a double-blind fashion. All subjects were on stable optimal medical therapy for at least 3 months before enrolment. At randomization and at study end, tumour necrosis factor-α and its soluble receptors TNFR-1 and TNFR-2 were measured and six-minute walk test and QoL were assessed. Cardiac magnetic resonance scanning was performed to evaluate cardiac dimensions and LVEF. Two patients died during follow-up. The remaining patients (14 randomized to placebo and 14 to micronutrients) were well matched for LV function, symptoms, and exercise capacity. At the end of the follow-up period, LV volumes were reduced in the intervention group with no change in the placebo group [$-$13.1 (17.1)% vs. $+$3.8 (10.0)%; $P < 0.05$]. LVEF increased by 5.3 $\pm$ 1.4% in the intervention group and was unchanged in the placebo group ($P < 0.05$). Patients taking micronutrients also had a significant improvement in QoL score between enrolment and study end [$+$9.5 (1.6)%; $P < 0.05$], whereas those taking placebo had a slight deterioration [$-$1.1 (0.8)%; $P = 0.12$]. Six-minute walk test and inflammatory cytokine levels remained unchanged in both groups.
Conclusion Long-term multiple micronutrient supplementation can improve LV volumes and LVEF and QoL scores in elderly patients with heart failure due to LV systolic dysfunction.

Introduction

Chronic heart failure (CHF) remains a common and serious problem, especially among the rising proportion of the population aged >70 despite recent advances in therapy.[1–6] The burden on health-care services, in terms of both resources and expenditure, is high.[7]

Patients with heart failure, especially if elderly, are prone to nutritional problems for a number of reasons. We have previously published an extensive review on this topic.[8] Appetite and food intake may be reduced because of changes in taste and smell, dietary advice on salt and calorie intake, social isolation, and possible congestion of the hepatic and splanchnic circulation. There is conflicting evidence of malabsorption. Reduced mobility may lead to reduced exposure to sunlight and therefore vitamin D synthesis. Loop diuretics may increase the urinary excretion of micronutrients, including thiamine and calcium.

On the other hand, patients with heart failure may be more susceptible to the effects of micronutrient deficiency because of increased oxidative stress (requiring antioxidant protection), impaired skeletal muscle function (possibly exacerbated by vitamin D deficiency), and impaired myocardial contraction (some severe micronutrient deficiencies can cause heart failure and therefore it is reasonable to expect that less severe deficiency may exacerbate existing cardiac dysfunction). Carnitine, Coenzyme Q10, and creatine

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supplementation have resulted in improved exercise capacity in some studies of heart failure, although not in others.[9–13] There is also conflicting evidence that supplementation with some micronutrients might retard the progression of coronary disease.[14–18]

Although in many countries, micronutrient supplementation is prescribed by doctors only for specific developing or established deficiency, the public purchase and self-administer large quantities at considerable cost. Presumably, sales are high because of perceived benefit, which may reflect a placebo or a real effect. Recently, there have been moves to tighten control of micronutrient sales directly to the public. For all these reasons, it seems very important to establish whether micronutrient supplements are an expensive placebo or effective therapy. A major problem with existing supplementation studies is that they tend to focus on just one micronutrient that, owing to complex metabolic pathways, may be ineffective or even exacerbate deficiencies in other pathways. Also, existing studies have not focused on elderly patients with heart failure, those at greatest risk of deficiency and its adverse consequences.[19,20]

The aim of the present study, therefore, was to assess the influence that long-term multiple micronutrient supplementations has on left ventricular (LV) function, levels of pro-inflammatory cytokines, and quality-of-life (QoL) in elderly patients with CHF.

Methods

Patients

We enrolled 32 patients aged >70 with stable CHF due to ischaemic heart disease into the study. We only approached consecutive patients under follow-up who we knew were suitable for the study. Of those approached, two declined to participate and two dropped out because of claustrophobia in the MRI scanner. Ischaemic heart disease was confirmed in all subjects by the presence of a history and electrocardiographic evidence of previous myocardial infarction or important coronary artery disease in at least two vessels on selective coronary angiography. Each patient gave informed, written consent prior to the involvement in the study, which was approved by the local ethics committee. Each individual was at the time of enrolment under follow-up in a community-based heart failure unit. CHF was defined as the presence of symptoms of fatigue or breathlessness on exertion and a LV ejection fraction (LVEF) on echocardiography of $\leq$35% with no other cause of breathlessness. Stability was defined as a diagnosis of at least 3 months in duration with no exacerbation or change in medication. Patients were on otherwise optimal therapy including diuretics, angiotensin-converting enzyme inhibitors (ACE-I), and β-blockers if tolerated. We excluded patients with neurological or inflammatory conditions or other significant chronic morbidity affecting QoL (e.g. severe rheumatoid arthritis) or requiring long-term systemic steroid or non-steroidal anti-inflammatory drugs therapy (except low-dose aspirin). We also excluded patients in persistent atrial fibrillation to optimize the reproducibility of our estimation of LV function.

At a baseline visit, each subject completed a QoL questionnaire, undertook a six-minute walk test following a standard protocol[21] and had blood samples taken for full blood count, renal, thyroid and liver function, N-terminal BNP, and cytokine measurements [tumour necrosis factor-α, (TNF-α) and soluble TNF receptor (sTNF-R)]. Within 5 days, each patient then underwent cardiac magnetic resonance (CMR) to assess cardiac function. Patients were reviewed every month.

Micronutrients

Subjects were randomized by a two-by-two method to receive either micronutrient supplementation or placebo capsules in a double-blind fashion. This was coordinated by a remote pharmacy with which the investigators had no contact during the study. The patients were asked to take four visually identical, opaque capsules per day of either placebo or micronutrients. *Table 1* shows the daily doses of the micronutrients received by those on active therapy. The placebo capsules contained cellulose. The micronutrients investigated were chosen in the light of results of previous human, animal, and basic science studies (reviewed in Witte *et al.*[8]). The doses of each were guided by previous studies and internationally recommended daily intakes (RDI) (*Table 1*). The pre-specified therapy duration was 1 year.

Assessment of cytokines and cytokine receptors

Blood samples were taken at baseline and at study end. Commercially available ELISA kits were used for assay of immune

Table 1 Doses of micronutrients, RDI, and upper safe daily intakes

Nutrient	Daily dose (four capsules)	RDI	Upper safe limit for total daily intake
Calcium	250 mg	800 mg	2500 mg
Magnesium	150 mg[a]	300 mg	700 mg
Zinc	15 mg	15 mg	30 mg
Copper	1.2 mg	1.2 mg	9 mg
Selenium	50 μg	65 μg	450 μg
Vitamin A	800 μg	800 μg	3300 μg
Thiamine	200 mg[a]	1.4 mg	No limit
Riboflavin	2 mg	1.5 mg	No limit
Vitamin B_6	200 mg[a]	2 mg	300 mg
Folate	5 mg[a]	200 μg	No limit
Vitamin B_{12}	200 μg	1 μg	No limit
Vitamin C	500 mg[a]	60 mg	2000 mg
Vitamin E	400 mg[a]	10 mg	900 mg
Vitamin D	10 μg[a]	5 μg	25 μg
Co-enzyme Q10	150 mg[a]	15 mg	No limit

[a]Doses taken from previous work[8] or RDI.

markers in venous samples. We chose TNF-α and IL-6 prospectively because of their clear relationship to adverse prognosis in CHF, and the availability of reliable detection kits. After centrifugation, samples were frozen at −70° C until analysis. Concentrations of TNF-α, TNFR-1, and TNFR-2 were determined by test kits (R&D Systems Minneapolis, USA), the lower limit of detection being 0.18, 25, and 2 pg/mL, respectively. Plasma concentrations of interleukin-6 (IL-6) were measured by Immulite (Random Access Immunoassay Analyzer, DPC Biermann, Bad Nauheim, Germany), the lower limit of detection being 1.0 pg/mL.

LV function

LV volumes, mass, and EF were measured using ECG-gated breath hold gradient cine CMR (GE, Norway, and Lister Healthcare, UK) within 5 days before enrolment and at study end. The analysis of anonymous and undated paired images was performed at the end of the study, using MASS MRI software (Medis, Leiden).

Quality-of-life

All patients self completed the EuroQoL heart failure QoL score tool at baseline, every month and at study end. This questionnaire, which incorporates evaluation of NYHA class and assesses a broad range of health-related and QoL issues relevant to heart failure, has been used in several large CHF surveys.[22] The patient is asked to respond to a series of 40 questions about symptoms of fatigue, breathlessness, ankle swelling, appetite, sleep, depression, mobility, and social activities. Each question is answered by grading the effect of each symptom. The answers are graded from 'not at all' (scoring 1) to 'very much' (scoring 0). Questions can be used individually to assess different aspects of the patient's life, while two general questions ask about the patient's perception of their overall health and overall QoL. In this way, a maximal score of 40 suggests an optimal QoL, whereas a score of 0 suggests a very poor QoL. The scores were then converted to a percentage of maximum at each time point. In a cohort of 250 individuals of a similar age chosen at random from the patient lists of local general practitioners with no history or symptoms of cardiovascular disease, the average QoL score was 36 (90%) [95% confidence intervals (CI) 35–37 (87–93%)] (Cleland *et al.*, unpublished results). The same scoring system has been used in the Euroheart Failure survey in which patients with definite CHF scored 59% (95% CI 57–60%),[22] and in a randomized controlled trial of revascularization in CHF.[23] We analysed these at baseline and compared them with the results at study end. By examining the symptom assessment every month, we were also able to look at longitudinal changes in QoL scores in those randomized to vitamins and those to placebo.

The study was terminated in September 2003. At the final visit, all tests were repeated and the CMR scans were performed within 5 days.

Statistical analysis

The primary outcome measure was pre-specified as an improvement in LV function (LVEF) as measured by MRI. CMR is highly reproducible allowing for small sample sizes.[24] A predicted average improvement of 10% in the active treatment arm, gave a sample size to confidently (90% power) detect a significant difference between populations of 30 patients (15 in each treatment arm).

The study code was not broken until all the data had been collected and analysed. Two-sided testing was used throughout the analysis. We recognized the risk of multiple testing, and the possible inflation of Type I error,[25] but as there is no consensus on how to deal with this,[26] we have not adjusted the data and the results should be interpreted accordingly.

We used Student's *t*-test to look at differences between the two groups of patients for continuous variables also for the changes in such variables between the two time points (Statview, SAS Institute). NYHA status was examined using the χ^2 test. The results of the QoL questionnaire were treated as continuous data after confirming normality of distribution using the Kolmogorow–Smirnov test. Results are presented as means (SD). A *P*-value <0.05 was considered significant, and absolute *P*-values have been included for important but non-significant variables.

Results

Of 32 patients enrolled, two were unable to tolerate the CMR scan. Our aim was to continue therapy for all patients for 1 year, but because of slow recruitment and the limited shelf-life of our supplements, follow-up was censored in September 2003. Patients were followed for an average of 295 days (inter-quartile range 105 days). Both groups were followed-up for the same length of time. The characteristics of the patients completing the study and their medication at enrolment are shown in *Table 2*. The patients in the two arms were similar in age, height, weight, EF, loop diuretic dose, NYHA status, TNF-α and TNF-R levels, and functional capacity. There was no change in β-blocker dose during the follow-up period. Two of the 30 patients (one in each group) enrolled into the study died in hospital during the follow-up period. One died of pneumonia (placebo group) and one as a consequence of extensive deep vein thrombosis and subsequent chest infection. QoL data of these patients from the time of enrolment to the last visit before death were included. There were no other adverse events. The capsules were well tolerated. There was no change in baseline renal, liver or thyroid function. The average dose of loop diuretic (frusemide equivalent) in the patients taking active capsules tend to decline during follow-up [63.5 (34) vs. 56 (31) mg], whereas that in the subjects taking placebo did not change [65 (23) vs. 67 (28) mg; $P = 0.09$ for the difference].

LV function

Table 3 shows the changes in CMR-measured variables in the two groups. LV end-diastolic and end-systolic volumes declined and EF improved in patient's randomized to micronutrient supplements compared with placebo (all $P < 0.05$) (*Table 3* and *Figure 1*).

Cytokines

The two groups were well matched for TNF-α, IL-6, and TNF-RI and II serum levels at baseline. There were no statistically significant changes in these variables with micronutrient supplementation (*Table 3*).

Exercise capacity

Baseline six-minute walk distance and change during follow-up were similar in the two groups.

Symptoms and QoL

There was no change in NYHA class in either group. The baseline scores, expressed as a percentage of maximum, for QoL are shown in *Table 3* and show the two groups to be well matched. Patients taking micronutrients had an increase in their QoL score [64.4 (13.4) vs. 73.9 (9.4); $P = 0.02$], and patients on placebo a decrease [67.2 (9.8) vs. 66.1 (7.9); $P =$ NS]. There is a significant difference in the change of QoL scores between the two groups. The

Table 2 Baseline characteristics

	Total study population ($n = 28$)	Active therapy ($n = 14$)	Placebo ($n = 14$)	*P*-value (between active and placebo)
Age (years)	75.4 (4.2)	74.2 (2.8)	75.5 (3.5)	0.75
Height (cm)	166 (10.7)	170 (9.4)	165 (10.0)	0.07
Weight (kg)	76.8 (13.8)	80.4 (9.2)	74.3 (12.4)	0.06
Average NYHA class	2.6 (0.5)	2.6 (0.4)	2.5 (0.4)	0.78
BMI (kg/m^2)	26.4 (3.2)	27.8 (2.4)	26.4 (3.5)	0.32
Heart rate (b.p.m.)	63 (17)	62 (28)	67 (25)	0.35
Mean BP	120/76	123/78	119/74	0.21
pVo_2 (mL/kg per minute)	19.8 (4.9)	19.1 (3.6)	18.8 (5.0)	0.33
6MWT (m)	287 (119)	279 (128)	267 (110)	0.54
LVEF (%)	26.1 (6.7)	25.6 (6.9)	26.6 (6.8)	0.71
LVEDV (mL)	217 (92)	222 (86)	212 (95)	0.23
SV (mL)	50.1 (17.9)	52.8 (18.1)	47.8 (11.8)	0.25
FEV_1 (L/min)	1.9 (0.6)	1.7 (0.6)	2.0 (0.7)	0.26
FVC (L)	2.8 (1.0)	2.7 (0.9)	2.8 (1.0)	0.62
Mean frusemide equivalent (mg)[a]	64 (35)	63 (34)	65 (23)	0.74
ACE-I/AIIA (*n*)	28	14	14	
Beta-blocker (*n*)	23	12	11	
Statin (*n*)	27	13	14	
Spironolactone (*n*)	7	4	3	
Serum sodium (mmol/L)	138 (3.5)	138 (3.3)	138 (3.7)	0.92
Serum creatine (μmol/L)	136 (68)	140 (78)	133 (59)	0.42
Haemoglobin (g/dL)	13.3 (1.9)	13.4 (1.7)	13.1 (2.0)	0.38
TSH (pmol/L)	1.8 (8.7)	1.9 (1.6)	1.7 (1.1)	0.34
Serum magnesium (mmol/L)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.72
Serum vitamin B_{12} (ng/L)	407 (179)	392 (192)	420 (171)	0.12
Serum ferritin (μg/L)	97 (95)	103 (108)	93 (87)	0.09
Serum folate (μg/L)	374 (150)	372 (147)	375 (155)	0.28
Serum calcium (mmol/L)	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)	0.56
Serum TNF-α (pg/mL)	5.4 (2.6)	5.6 (3.2)	5.1 (2.0)	0.11
Serum TNF-R1 (pg/mL)	1192 (391)	1228 (432)	1161 (363)	0.08
Serum TNF-R II (pg/mL)	1974 (648)	1951 (618)	1993 (694)	0.10
Baseline QoL	66.3 (8.3)	64.4 (13.4)	67.2 (9.8)	0.34

Values are mean (SD). NYHA, New York Heart Association classification (χ^2 *P*-value); BMI, body mass index; pVo_2, peak oxygen consumption; 6MWT, six-minute walk test distance; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ns, non-significant; AIIA, angiotensin II inhibitor; TSH, thyroid-stimulating hormone; sTNF-RI, soluble tumour necrosis factor-receptor 1; sTNF-RII, soluble tumour necrosis factor-receptor 2.

[a]The mean daily dose at enrolment of frusemide or frusemide equivalent (1 mg bumetanide = 40 mg frusemide) is given (SD).

scores started to diverge after 6 months (*Figure 2*). Further analysis of the data suggested that the difference in overall score was driven predominantly by the improvements in scores for exertional breathlessness, quality of sleep, daytime concentration, and overall QoL ratings.

Discussion

This is the first study to investigate the effects of multiple micronutrient supplementations on LV function and QoL in patients with heart failure. The study suggests that such treatment improves LV function when assessed using CMR imaging, an accurate and highly reproducible method for assessing ventricular volumes that allows interventions to be tested in a small number of patients.[24] Improvement in ventricular function was associated with some evidence of improved patient well-being.

Previous studies of micronutrient supplements in heart failure have only randomized patients to a single agent. This reflects bias against the use of multiple supplements on the grounds that if improvement is observed, the mechanism will be unclear. However, using single supplements to correct only one deficiency when multiple exist may be useless and could be harmful by causing the accumulation of harmful metabolic products. On the other hand, micronutrients may have synergistic effects. For example, vitamin C is involved in the regeneration of cell-membrane bound vitamin E. Testing single substances in a series of randomized controlled trials would not only take a long time but could be misleading. Starting with a broad range supplement circumvents these problems and was also the strategy of a recent multivitamin supplementation study in patients with HIV infection.[27] The value of identifying elements to be omitted without loss of benefit can then be assessed. This study reflects the first step on that route. It is possible that many components of our micronutrient cocktail were unnecessary or that further components may be added for greater effect.

Severe thiamine deficiency is a well-documented cause of heart failure. It has also been suggested that high doses of

Table 3 CMR variables, TNF- α, selected micronutrients and QoL scores (% of maximum) at baseline and study end with micronutrient supplementation and placebo

	Baseline active therapy group ($n = 14$)	Post-active therapy ($n = 14$)	Baseline placebo group ($n = 14$)	Post-placebo ($n = 14$)	*P*-value for change between active and placebo
LVESV (mL)	169 (83)	138 (86)	164 (87)	172 (81)	0.02
LVEDV (mL)	222 (86)	193 (90)	212 (95)	224 (91)	0.03
LV mass diastole (g)	160 (38)	158 (43)	143 (34)	154 (41)	0.08
LV mass systole (g)	174 (39)	167 (41)	158 (33)	166 (45)	0.08
SV (mL)	52.8 (18.1)	55.3 (20.1)	47.8 (11.8)	52.4 (13.5)	0.17
LVEF (%)	25.6 (6.9)	30.9 (7.1)	26.6 (6.8)	26.2 (7.2)	0.03
Heart rate (b.p.m.)	62 (28)	59 (29)	67 (25)	66 (16)	0.12
Serum magnesium (mmol/L)	0.9 (0.1)	1.1 (0.1)	0.9 (0.1)	0.5 (0.1)	0.04
Serum vitamin B_{12} (ng/L)	392 (192)	409 (194)	420 (171)	409 (162)	0.02
Serum ferritin (μg/L)	103 (108)	576 (261)	93 (87)	77 (68)	0.009
Serum folate (μg/L)	372 (147)	400 (20)	375 (155)	285 (124)	0.008
TNF-α (pg/mL)	5.6 (3.2)	5.7 (4.5)	5.1 (2.0)	5.1 (2.1)	0.86
sTNF-RI (pg/mL)	1228 (432)	1207 (443)	1161 (363)	1450 (374)	0.16
sTNF-RII (pg/mL)	1951 (618)	2250 (643)	1993 (694)	2504 (716)	0.31
QoL	64.4 (13.4)	73.9 (1.6)*	67.2 (9.8)	66.1 (11.1)	0.02

Values are means (SD). LVESV, left ventricular end-systolic volume, other abbreviations as for *Table 2*.

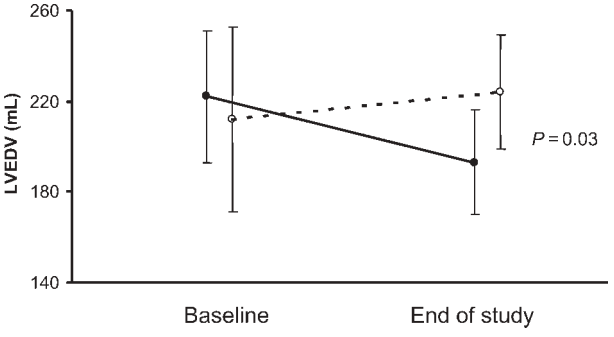

Figure 1 Change in left ventricular end-diastolic volume with placebo (unfilled circles and dashed line) and micronutrient supplementation (filled circles and solid line), (error bars are SD).

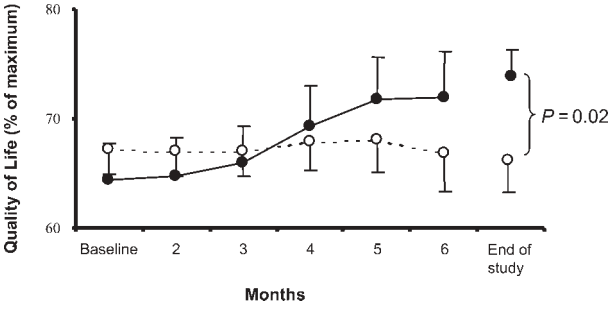

Figure 2 Quality of life score (percentage of maximum) during study period for patients taking placebo (unfilled circles and dashed line) or micronutrient supplementation (filled circles and solid line), (error bars are SD).

thiamine (200 mg daily) can improve cardiac function in patients with CHF receiving loop diuretics, which cause an increase in urinary excretion.[28,29]

One potential mechanism of benefit from micronutrient supplementation is the reduction of oxidative stress. Markers of oxidative stress are elevated in heart failure patients and correlate with functional class, reduced exercise tolerance, lower antioxidant levels, and indices of worse prognosis.[30,31] Patients with heart failure have lower levels of co-enzyme Q_{10}, a powerful endogenous anti-oxidant, in their myocardium compared with controls.[32] Low plasma co-enzyme Q10 levels are associated with an increased mortality in heart failure.[33] Supplementation with co-enzyme Q_{10} at a variety of doses in uncontrolled studies has shown improvements in EF, exercise tolerance, and NYHA status. However, data from randomized studies are less consistent, although studies using higher doses ($\geq$2 mg/kg/day) were more likely to show benefit.[9–13] Recent meta-analyses have clarified the situation somewhat suggesting benefits on symptoms and cardiac output and a trend to improved mortality in patients with CHF.[34,35] Nevertheless, the reduction of the synthesis of co-enzyme Q_{10} by statins seems to be of sufficient concern that regulatory authorities required plasma co-enzyme Q_{10} measurements in a substantial proportion of patients in a large mortality trial of rosuvastatin in heart failure.

Vitamin C, vitamin E, magnesium, selenium, and zinc also appear to have anti-oxidant effects and may affect cardiac function.[36–39] Vitamin C acutely improves the ejection duration in patients with CHF independent of heart rate.[40] Vitamin C also reduces apoptosis in cardiomyocytes in rats with experimental heart failure.[41] Vitamin D and calcium deficiency can impair myocardial contractility, but the effects of supplementation in humans are unknown.[42] The only study examining the effects of vitamin E in CHF patients was neutral.[43]

Peripheral vasodilation with a reduction in peripheral vascular resistance and afterload might also contribute to improved cardiac function. Selenium can cause vascular smooth muscle relaxation,[44] and vitamins C and E can improve endothelial-dependent vasodilation.[45,46] The B vitamins reduce homocysteine levels. Prolonged exposure to high homocysteine levels leads to a fall in nitric oxide production and impaired peripheral vasodilation.[47]

All our patients had coronary disease. Selected micronutrient supplementation in patients at risk of or with established coronary artery disease has generally not been

shown to improve outcome.[16–18] However, few of these patients had heart failure and therefore may have had a lower risk of micronutrient deficiency or susceptibility and, as noted earlier, the results of studies using single agent supplements may be misleading.

There was no difference in NYHA status after micronutrient supplementation, but the study population was small. Our patients also completed QoL questionnaires at the end of every 1-month-follow-up period. The QoL of the patients improved significantly with the micronutrient supplementation.

The QoL score improved in our patients predominantly due to improved scores for fatigue and breathlessness during daily activity, improved quality of sleep, and improved daytime concentration. However, we did not observe an improvement in NYHA score or distance walked on the six-minute walk test. The effects of supplements on symptoms could reflect a chance finding, as multiple measurements were made and the QoL tool that we used has not yet been fully validated. However, the primary outcome measure of this study, LVEF, did improve and improved cardiac function might be expected to be associated with improved symptoms. It is possible that the failure to demonstrate an improvement in NYHA class or walk-test distance reflects inadequate study size rather than lack of effect, given the variability of these tests and probably only a modest benefit.

Conclusions

When added to conventional therapy with β-blockers and ACE-Is multiple micronutrient supplementations may improve LV function and patient well-being. Further trials are warranted with larger numbers of patients and a longer follow-up period.

Limitations

Although carried out in a randomized, prospective, and double-blind fashion, the present study involved small number of patients and the data must be viewed in the light of this. We also did not measure blood levels of all the micronutrients to assess compliance, although the changes in the ferritin, vitamin B_{12}, and folate levels in the patients randomized to the micronutrient combination suggest that they took them.

References

1. Cowie MR, Mosterd A, Wood DA. The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208–225.
2. Braunwald E. Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;**337**:1360–1369.
3. Brown A, Cleland JGF. Influence of concomitant disease on patterns of hospitalisations in patients with heart failure from Scottish hospitals in 1995. *Eur Heart J* 1998;**19**:1063–1069.
4. Cleland JGF, Swedberg K, Poole-Wilson PA. Successes and failures of current treatment of heart failure. *Lancet* 1998;**352**(Suppl. 1):19–28.
5. McMurray J, McDonagh T, Morrison CE, Dargie HJ. Trends in hospitalisation for heart failure in Scotland 1980–1990. *Eur Heart J* 1993;**14**:1158–1162.
6. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, McGlynn EA, Ware JE Jr. Functional status and well-being of patients with chronic conditions. *JAMA* 1989;**262**:907–913.
7. Stewart S, Horowitz JD. Detecting early clinical deterioration in chronic heart failure patients post-acute hospitalisation—a critical component of multidisciplinary, home-based intervention? *Eur J Heart Fail* 2002;**4**:345–351.
8. Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. *J Am Coll Cardiol* 2001;**37**:1765–1774.
9. Morisco C, Trimarco B, Condorelli M. Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicentre randomised study. *Clin Invest* 1993;**71**:S134–S136.
10. Hofman-Bang C, Rehnqvist N, Swedberg K, Wiklund I, Astrom H. Coenzyme Q10 as an adjunctive treatment of chronic congestive heart failure. The Q10 study group. *J Card Fail* 1995;**2**:101–107.
11. Jeejeebhoy F, Keith M, Freeman M, Barr A, McCall M, Kurian R, Mazer D, Errett L. Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am Heart J* 2002;**143**:1092–1100.
12. Khatta M, Alexander BS, Krichten CM, Fisher ML, Freudenberger R, Robinson SW, Gottlieb SS. The effect of coenzyme Q10 in patients with congestive heart failure. *Ann Intern Med* 2000;**132**:636–640.
13. Watson PS, Scalia GM, Galbraith A, Burstow DJ, Bett N, Aroney CN. Lack of effect of coenzyme Q10 on left ventricular function in patients with congestive cardiac failure. *J Am Coll Cardiol* 1999;**33**:1549–1552.
14. Knekt P, Ritz J, Pereira MA, O'Reilly EJ, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Rimm EB, Ascherio A. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr* 2004;**80**:1508–1520.
15. Voutilainen S, Virtanen JK, Rissanen TH Alfthan G, Laukkanen J, Nyyssonen K, Mursu J, Valkonen VP, Tuomainen TP, Kaplan GA, Salonen JT. Serum folate and homocysteine and the incidence of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr* 2004;**80**:317–323.
16. The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:154–160.
17. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:23–33.
18. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;**354**:447–455.
19. Cleland JG, Thygesen K, Uretsky BF, Armstrong P, Horowitz JD, Massie B, Packer M, Poole-Wilson PA, Ryden L; ATLAS investigators. Cardiovascular critical event pathways for the progression of heart failure; a report from the ATLAS study. *Eur Heart J* 2001;**22**:1601–1612.
20. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;**24**:442–463.
21. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J.* 1985;**132**:919–923.
22. Cleland JG, Swedberg K, Cohen-Solal A Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Preda I, van Gilst WH, Widimsky J, Mareev V, Mason J, Freemantle N, Eastaugh J. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. *Eur J Heart Fail* 2000;**2**:123–132.
23. Cleland JG, Freemantle N, Ball SG, Bonser RS, Camici P, Chattopadhyay S, Dutka D, Eastaugh J, Hampton J, Large S, Norell MS, Pennell DJ, Pepper J, Sanda S, Senior R, Smith D. The heart failure revascularisation trial (HEART): rationale, design and methodology. *Eur J Heart Fail* 2003;**5**:295–303.
24. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodelling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2000;**2**:271–278.
25. Altman DG, Machin D, Bryant TN, Gardner MJ. *Statistics with Confidence*. 2nd ed. London: BMJ; 2000.
26. Perneger TV. What's wrong with Bonferonni adjustments? *Br Med J* 1998;**316**:1236–1238.

27. Fawzi WW, Msamanga GI, Spiegelman D, Wei R, Kapiga S, Villamor E, Mwakagile D, Mugusi F, Hertzmark E, Essex M, Hunter DJ. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004;**351**:23–32.
28. Shimon I, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, Rosenthal T, Motro M, Halkin H, Ezra D. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *Am J Med* 1995;**98**:485–490.
29. Nakajima H, Miyagi Y, Sasayama S. Effects of thiamine (vitamin B1) on exercise capacity in patients with congestive heart failure. *J Am Coll Cardiol* 1986;**74**(Suppl. II):153.
30. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol* 1998;**31**:1352-1356.
31. Nishiyama Y, Ikeda H, Haramaki N, Yoshida N, Imaizumi T. Oxidative stress is related to exercise intolerance in patients with heart failure. *Am Heart J* 1998;**135**:115–120.
32. Kitamura N, Yamaguchi A, Otaki M. Myocardial tissue level of co-enzyme Q10 in patients with cardiac failure. In: Folkers K, Yamamura Y, eds. *Biomedical and Physical Aspects of Coenzyme Q*. Vol. **4**. Amsterdam: Elsevier; 1984. p243–257.
33. Jameson S. Statistical data support prediction of death within 6 months on low levels of coenzyme Q10 and other entities. *Clin Invest* 1993;**71**:S137–S139.
34. Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. *Mol Aspects Med* 1997;**18**(Suppl):S159–S168.
35. Rosenfeldt F, Hilton D, Pepe S, Krum H. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. *Biofactors* 2003;**18**:91–100.
36. Kang YJ. The antioxidant function of metallothionein in the heart. *Proc Soc Exp Biol Med* 1999;**222**:263–273.
37. Wu F, Altura BT, Gao J, Barbour RL, Altura BM. Ferrylmyoglobin formation induced by acute magnesium deficiency in perfused rat heart causes cardiac failure. *Biochim Biophys Acta* 1994;**1225**:158–164.
38. Coudray C, Charlon V, de Leiris J, Favier A. Effect of zinc deficiency on lipid peroxidation status and infarct size in rat hearts. *Int J Cardiol* 1993;**41**:109–113.
39. de Lorgeril M, Salen P, Accominotti M, Cadau M, Steghens JP, Boucher F, de Leiris J. Dietary and blood antioxidants in patients with chronic heart failure. Insights into the potential importance of selenium in heart failure. *Eur J Heart Fail* 2001;**3**:661–669.
40. Schmitt M, Nightingale AK, Ellis GR. Vitamin C acutely improves ejection duration in chronic heart failure (CHF) patients in a heart rate independent fashion. *Eur J Heart Fail* 2000;**2**:Abstract P52/10423.
41. Rossig L, Hoffmann J, Hugel B, Mallat Z, Haase A, Freyssinet JM, Tedgui A, Aicher A, Zeiher AM, Dimmeler S. Vitamin C inhibits endothelial cell apoptosis in congestive heart failure. *Circulation* 2001;**104**:2182–2187.
42. Weisshaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. Direct and indirect effects. *Am J Physiol* 1987;**253**: E675–E683.
43. Keith ME, Jeejeebhoy KN, Langer A, Kurian R, Barr A, O'Kelly B, Sole MJ. A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. *Am J Clin Nutr* 2001;**73**:219–224.
44. May SW, Pollock SH. Selenium-based antihypertensives. Rationale and potential. *Drugs* 1998;**56**:959–964.
45. Hornig B, Arakawa N, Kohler C, Drexler H. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. *Circulation* 1998;**97**:363–368.
46. Plotnick GD, Corretti MC, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependant brachial artery vasoactivity following a single high-fat meal. *JAMA* 1997;**278**:1682–1686.
47. Stamler JS, Osborne JA, Jaraki O. Adverse vascular effects of homocysteine are modulated by endothelial derived relaxing factor and related oxides of nitrogen. *J Clin Invest* 1993;**91**:308–318.