European Heart Journal (2005) **26**, 2215–2217
doi:10.1093/eurheartj/ehi490

Editorial

Importance of nutrition in chronic heart failure patients

Michel de Lorgeril[1,2]*, Patricia Salen[1,2], and Pascal Defaye[1,2]

[1] *Laboratoire Nutrition, Vieillissement et Maladies Cardiovasculaires (NVMCV), Université Joseph Fourier de Grenoble, Grenoble, France and* [2] *Department of Cardiology, University Hospital, Grenoble, France*

Online publish-ahead-of-print 23 September 2005

This editorial refers to 'The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure'† by K.K.A. Witte *et al.*, on page 2238

The incidence of chronic heart failure (CHF), the common end-result of most cardiac diseases, is increasing steadily in most countries.[1] In recent years, most of the research efforts on CHF have focused on drug therapies and devices (implantable defibrillators and resynchronization), and little attention has been paid to non-pharmacological approaches, and particularly to nutrition. Only recently, it has been recognized that increased oxidative stress, for instance, may be involved in the pathogenesis of CHF.[2] The intimate link between diet and oxidative stress is obvious, knowing that our body derives its main antioxidant defences from essential nutrients (meaning that they are necessarily obtained from foods).

Although it is generally considered that a diet high in sodium is harmful (and may result in acute decompensation of CHF through a volume overload mechanism), little is known about the other aspects of diet in CHF, in terms of both general nutrition and micronutrients, such as vitamins and minerals. In CHF patients, it is important not only to properly screen for and aggressively treat the traditional risk factors of coronary heart disease (CHD) (the main cause of CHF), such as high blood pressure and cholesterol (because they can aggravate the syndrome), but also to recognize and correct malnutrition and deficiencies in specific micronutrients. Some macronutrients such as essential fatty acids (discussed subsequently) may even be critical.

Witte *et al.*[3] report the results of a double-blind trial testing the effects of micronutrient supplementation in patients with overt CHF. In spite of some obvious limitations (small sample size, no biological measurements to evaluate the degree of malnutrition in these patients, and no evaluation of their dietary habits, a major confounder in such a trial), these data must be taken very seriously. In fact, this is the first controlled dietary trial in CHF patients, and the authors report a significant effect on left ventricular (LV) function. Quality-of-life (QoL) was also apparently improved. The authors rightly lay stress on the fact that they used a cocktail of micronutrients rather than a single agent. Actually, nutrients are not drugs and, as recently emphasized, 'nutrition is not pharmacology'.[4] This is most important because, except for a few cases (like thiamine deficiency), the nutritional approach necessarily involves multiple factors (any food contains many nutrients that have been assembled into that specific food by Mother Nature, for very good reasons), and because most nutrients are biologically active in the body through synergistic effects. Let us take some examples inspired by Witte's work to illustrate the point.

Witte *et al.*[3] first set forth that one potential beneficial mechanism in their trial was the reduction of oxidative stress. Indeed, their cocktail contained several antioxidants including zinc, selenium, vitamins A, C, and E, and coenzyme Q10. The vital importance of micronutrients for health and the fact that several micronutrients have antioxidant properties are now fully recognized. Antioxidants may have a direct action (e.g. vitamins C and E) or act as components of antioxidant enzymes, like zinc in superoxide dismutase or selenium in glutathione peroxidase. It is now widely believed (but still not causally demonstrated) that diet-derived antioxidants (and not high-dosage supplementation) may play a role in the development (and thus in the prevention) of CHF. For instance, clinical and experimental studies have suggested that CHF may be associated with increased free radical formation and reduced antioxidant defences (de Lorgeril *et al.*[5] and references therein). Reduced antioxidant defences result from a combination of insufficient dietary intake and excessive utilization of specific antioxidants without adequate recycling or replacement. An important practical point is whether deficiencies in specific micronutrients may cause or at least aggravate CHF. The actual prevalence of such deficiencies among CHF patients is unknown. Whether we should systematically screen for them also remains unclear, although some preliminary data tend to encourage us to do so (see below about selenium). Also, we do not know whether the association of several marginal deficiencies that do not individually result in CHF may cause CHF, especially in the elderly. There is no room here to fully expose current knowledge in that field.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

*Corresponding author: Laboratoire NVMCV, UFR de Médecine et Pharmacie, Domaine de la Merci, 38706 La Tronche, Grenoble, France.
E-mail address: michel.delorgeril@ujf-grenoble.fr

† doi:10.1093/eurheartj/ehi442

However, restricting our comments to human data only, we can say that low magnesium, for instance, is often associated with a poor prognosis of CHF, and that correcting magnesium levels (e.g. in anorexia nervosa) leads to an improvement in cardiac function. Low serum and high urinary zinc levels in CHF patients is another example. This may be an effect of diuretic drugs, but no data are available on the clinical effect of zinc supplementation in this context. Also, selenium deficiency has been identified as a major factor in the aetiology of certain non-ischaemic CHF syndromes, especially in low-selenium soil areas such as Eastern China and Western Africa.[5] In Western countries, cases of congestive cardiomyopathy associated with low antioxidant nutrients (vitamins and trace elements) have been reported in malnourished HIV-infected patients and in subjects on chronic parenteral nutrition.[5] Selenium deficiency is also a risk factor for peripartum cardiomyopathy. In China, an endemic cardiomyopathy called Keshan disease seems to be a direct consequence of selenium deficiency. Although the mechanism by which selenium deficiency results in CHF remains an open question, recent data suggest that selenium may be involved in skeletal (and cardiac) muscle deconditioning (and in CHF symptoms such as fatigue and low exercise tolerance) rather than in LV dysfunction.[5] As a matter of fact, we have found that CHF patients had a low selenium status (low dietary intake and low blood level) relative to healthy controls, and that blood selenium was strongly related to maximum oxygen consumption and exercise tolerance, but not to LV function.[5] This is not surprising, knowing that in the Keshan area, the selenium status matches clinical severity rather than the degree of LV dysfunction as assessed by echocardiographic studies.[5] When the selenium levels of Keshan residents were raised to the typical levels in non-endemic areas, the mortality rate declined significantly but clinically latent cases were still found and the echocardiographic prevalence of the disease remained high. In summary, what we learn from Keshan disease and other studies conducted elsewhere[5] is that even a mild deficiency in selenium can influence the clinical severity of the disease in patients with a known cause of CHF (tolerance to exercise and QoL). These data should be a strong incentive to launch studies testing the effects of natural antioxidants on the clinical severity of CHF. In the meantime, however, physicians would be well advised to measure selenium in patients with an exercise inability disproportionate to their cardiac dysfunction.

The micronutrient cocktail tested by Witte also contained very large amounts of B-group vitamins (and magnesium, which interacts with vitamin B6), and blood levels increased significantly in the treatment group. This may have decreased the levels of homocysteine, an aminoacid known to have negative inotropic effects,[6] probably mediated through an effect on endothelial function, but this was not measured in Witte's study. Thus, in addition to the antioxidant effects, the micronutrients tested by Witte may have improved LV function by reducing homocysteine levels. This is very important, because homocysteine was found to be increased in CHF patients (20.5 ± 2.5 μmol/L) when compared with healthy controls (13.3 ± 1.1; $P = 0.01$), in association with relatively low levels of vitamin B6, B9, B12, and magnesium.[5] Reducing homocysteine by correcting multiple marginal vitamin B deficiencies may be key to the treatment of many CHF patients.

Finally, an epidemiological study has recently shown that the intake of very long chain omega-3 fatty acids (VLC-OM3) was associated with a lower CHF risk, with a 37% lower risk in the highest quintile of intake than in the lowest.[7] This is in line with the well-known cardioprotective effect of VLC-OM3[4] and with numerous experimental studies[7] showing that VLC-OM3 have a favourable effect on LV function. As a matter of fact, large trials have been launched to test the hypothesis that VLC-OM3 may reduce mortality in CHF patients. VLC-OM3 can be obtained from fatty fish or fish oil, or alternatively from their vegetable precursor (alpha-linolenic acid) through endogenous desaturation (and elongation) of the fatty acid carbon chain. The latter pathway dominates in populations with low fish consumption, which is the case in most Western populations. Interestingly, certain micronutrients present in Witte's micronutrient cocktail, in particular zinc, magnesium, and vitamin B6, are co-factors of delta-5 and delta-6 desaturases. A deficiency in these nutrients was shown to reduce the synthesis of arachidonic acid and of VLC-OM3 from their essential vegetable omega-6 and omega-3 precursors.[8–10] In other words, a low intake of any of these desaturase co-factors (or marginal but combined deficiencies in these nutrients) may decrease the synthesis of VLC-OM3 and result in a higher risk of CHF and other cardiac complications, such as sudden cardiac death,[4] which is the main cause of death in CHF patients. Thus, adequate micronutrient availability is necessary to favourably influence essential omega-3 fatty acid metabolism, and it is likely that the micronutrient cocktail tested by Witte did so. Further studies are required to test whether dietary advices (with or without supplements) may prevent clinical complications of CHF.

In conclusion, as shown by these examples, there is growing evidence that nutrition might be a critical factor in the prognosis and treatment of CHF. Further studies, including randomized trials, are urgently needed to unveil the main dietary determinants and major metabolic pathways upon which we could act by monitoring and managing the diet of our CHF patients. In any case, because nutrition is a huge risk factor of CHD and also the main cause of CHF, physicians involved in CHF care should consider their patients' dietary habits as a primary target of treatment.

Conflict of interest: none declared.

References

1. Cowie MR, Mostred A, Wood DA, Decker JW, Poole-Wilson PA, Sutton CG, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208–225.
2. 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.
3. Witte KKA, Nikitin NP, Parker AC, von Haehling S, Volk H-D, Anker SD, Clark AL, Cleland JGF. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. *Eur Heart J* 2005;**26**:2238–2244. First published on August 4, 2005, doi:10.1093/eurheartj/ehi442.
4. de Lorgeril M, Salen P. Fish and n-3 fatty acids for the prevention and treatment of coronary heart disease: nutrition is not pharmacology. *Am J Med* 2002;**112**:316–319.

5. de Lorgeril M, Salen P, Accominotti M, Cadau M, Steghens JP, Boucher F, de Leiris J. Dietary 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.
6. Kennedy RH, Owings R, Shekhawat N, Joseph J. Acute negative inotropic effects of homocysteine are mediated via the endothelium. *Am J Physiol Heart Circ Physiol* 2004;**287**:H812–H817.
7. Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J Am Coll Cardiol* 2005;**45**:2015–2021.
8. Clejan S, Castro-Magana M, Collipp PJ, Jonas E, Maddaiah VT. Effects of zinc deficiency and castration on fatty acid composition and desaturation in rats. *Lipids* 1982;**17**:129–135.
9. Mahfouz MM, Kummerow FA. Effects of magnesium deficiency on delta-6 desaturase activity and fatty acid composition of rat liver microsomes. *Lipids* 1989;**24**:727–732.
10. Bordoni A, Hrelia S, Lorenzini A, Bergami R, Cabrini L, Biagi PL, Tolomelli B. Dual influence of aging and vitamin B6 on delta-6 desaturation of essential fatty acids in rat liver microsomes. *Prostaglandin Leukot Essent Fatty Acids* 1998;**58**:417–420.