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# MICRONUTRIENTS, INFLAMMATION AND CONGESTIVE HEART FAILURE AMONG THE ELDERLY: NUTRITIONAL PERSPECTIVES ON PRIMARY PREVENTION AND CLINICAL TREATMENT

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## SUMMARY

**1. The aim of the present study was to examine the associations between micronutrients, inflammation and the prevalence of congestive heart failure (CHF) in the elderly aged ≥ 65 years, using the US National Health and Nutrition Examination Surveys.**

**2. After adjusting for age, gender, race/ethnicity and other covariates, subjects with decreased folate and vitamin $B_{12}$ intake and with elevated serum levels of inflammatory biomarkers (C-reactive protein and total homocysteine) had significantly higher risk of CHF than their counterparts.**

**3. Elderly women had a significantly higher prevalence of hypovitaminosis D (serum 25-Hydroxyvitamin(OH)D < 20 ng/mL) than men (37 *vs* 23%, respectively; $P < 0.01$). Elderly African Americans had the lowest mean levels of serum 25(OH)D (20.9 ng/mL) compared with Mexican Americans (24.1 ng/mL) and Caucasians (28.2 ng/mL).**

**4. Subjects with decreased serum 25(OH)D levels had a significantly higher prevalence of CHF than those who had higher serum 25(OH)D, for both men and women. Multivariate logistic regression analyses indicated that a decrease of 10 ng/mL in the serum 25(OH)D level was associated with an increased relative risk (95% confidence interval) of 1.22 (1.08–1.36) for CHF.**

**5. Subjects with a micronutrient insufficient status and with coexisting metabolic syndrome had an even higher risk of CHF.**

**Key words: congestive heart failure, folate, vitamin $B_{12}$, vitamin D.**

## INTRODUCTION

It is estimated that 4.9 million Americans live with congestive heart failure (CHF) and 550 000 new cases are diagnosed yearly. Elderly individuals are at particularly high risk of the development of CHF. Although epidemiological and experimental evidence is emerging that demonstrates nutritional factors may play a critical role in the development and prognosis of the disease, the influence of nutrition on CHF phenotypes is poorly understood.[1–4] The present study aimed to examine micronutrients and inflammation status in relation to the risk of CHF among elderly American populations.

## METHODS

To examine the associations of micronutrient intake (folate and vitamin $B_{12}$) and serum inflammatory biomarkers (C-reactive protein and homocysteine) with risk of CHF, we used data from the US National Health and Nutrition Examination Survey (NHANES 1999–2002).[5,6] To examine the association between serum vitamin D concentration (assessed by serum 25-Hydroxyvitamin(OH)D levels) and the risk of CHF, we used the NHANES III (1988–1994)[7] because serum vitamin D measures were not available in the NHANES 1999–2002. In the NHANES surveys, CHF was defined as self-reported physician-diagnosed cases. Diet micronutrient intake was estimated on the basis of one 24 h dietary recall. Biochemical biomarkers were measured from a fasting blood sample, in which the serum 25(OH)D concentration (the circulating form of vitamin D in the blood) was assayed using radioimmunoassay kits (DiaSorin, Stillwater, MN, USA). In data analyses, stratification for metabolic syndrome (MS; classified according to World Health Organization criteria[8]) was conducted because more than 20% of CHF patients had coexisting MS. The final sample of the present study included 2170 participants in NHANES 1999–2002 and 3998 in NHANES III, aged ≥ 65 years. All analyses were conducted using SAS version 9.0 (SAS Institute, Cary, NC, USA).

## RESULTS

The prevalence of CHF was found to be 10% in NHANES III and 11% in NHANES 1999–2002. Subjects with MS had a significantly higher prevalence of CHF than those without MS (24 *vs* 6.4%, respectively; $P < 0.0001$). The prevalence of CHF was 7.8% in Caucasians, 9.3% in African Americans and 12.6% in Mexican Americans.

Subjects with lower folate and vitamin $B_{12}$ intake and with elevated serum C-reactive protein (CRP) and total homocysteine had significantly higher risk of CHF than their counterparts. The multi-adjusted odds ratio (95% confidence interval (CI)) for CHF with decreased diet folate intake was 1.60 (1.15–2.23) in the total study population and 1.69 (1.03–2.76) among those with MS (Table 1).

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**Table 1** Estimated risks of having congestive heart failure among the elderly (aged ≥ 65 years) in relation to decreased micronutrient intake and elevated serum levels of inflammatory biomarkers

| | Odds ratios (95% CI) | | |
|---|---|---|---|
| | Crude | Age-adjusted | Multi-adjusted† |
| In total sample ($n = 2170$) | | | |
| Folate intake (< 400 mcg *vs* ≥ 400 mcg) | 1.80 (1.30–2.48) | 1.77 (1.28–2.44) | 1.60 (1.15–2.23) |
| Vitamin $B_{12}$ intake (< 6 mcg *vs* ≥ 6 mcg) | 1.89 (1.32–2.71) | 1.68 (1.18–2.61) | 1.65 (1.10–2.45) |
| CRP (> 0.3 mg/dL *vs* ≤ 0.3 mg/dL) | 4.04 (3.08–5.31) | 2.81 (2.09–3.77) | 2.68 (1.00–3.62) |
| tHcy (> 12 *vs* ≤ 12 μmol/L) | 5.93 (4.46–7.88) | 5.36 (4.02–7.16) | 5.25 (3.91–7.06) |
| In those with MS ($n = 583$) | | | |
| Folate intake (< 400 mcg *vs* ≥ 400 mcg) | 2.00 (1.24–3.23) | 1.84 (1.13–2.99) | 1.69 (1.03–2.76) |
| Vitamin $B_{12}$ (< 6 mcg *vs* ≥ 6 mcg) | 1.78 (1.03–3.08) | 1.77 (1.02–3.07) | 1.76 (1.03–3.16) |
| CRP (> 0.3 mg/dL *vs* ≤ 0.3 mg/dL) | 3.89 (2.43–6.23) | 4.04 (2.51–6.02) | 3.81 (2.35–6.17) |
| tHcy (> 12 *vs* ≤ 12 μmol/L) | 7.16 (4.65–11.03) | 6.66 (4.31–10.29) | 6.65 (4.25–10.39) |

†Multi-adjusted for age, sex, race/ethnicity, education levels and body mass index. To run full models, missing data were estimated using average method with stratification of case and non-case groups.

CRP, C-reactive protein; tHcy, total homocysteine; MS, metabolic syndrome; CI, confidence interval.

Indicators of population-attributable risk suggested that an average of 25–33% of CHF could be prevented by improved intake of these two micronutrients.

The prevalence of hypovitaminosis D (defined as 25(OH)D < 20 ng/mL) was 23% in men and 37% in women. Mean (±SD) serum 25(OH)D concentrations were 28.2 ± 10.3 ng/mL in Caucasians, 20.9 ± 9.9 ng/mL in African Americans and 24.1 ± 9.8 ng/mL in Mexican Americans. Subjects with CHF had significantly lower vitamin D levles than those without CHF in both men (24.3 *vs* 26.1 ng/mL, respectively; $P = 0.015$) and women (19.3 *vs* 22.7 ng/mL, respectively; $P < 0.001$). Correlation analyses (adjusting for age and sex) indicated that vitamin D was significantly and positively correlated with vitamin C ($r = 0.22$; $P < 0.001$), vitamin E ($r = 0.21$; $P < 0.001$) and folate ($r = 0.28$, $P < 0.001$) and negatively associated with homocysteine ($r = –0.11$; $P < 0.001$) and CRP ($r = –0.06$, $P < 0.05$). Adjusting for age, sex, body mass index, glomerular filtration rate and γ-glutamyltranspeptidase level (an indicator of liver function), logistic regression analyses indicated that a decrease of 10 ng/mL in serum vitamin D was associated with an increased relative risk (95% CI) of 1.22 (1.08–1.36) for CHF. Elderly in the lowest quartile for vitamin D (< 18 ng/mL) had a 2.25-fold higher risk of CHF than those in the highest quartile (≥ 32 ng/mL) and the associations were independent of age, sex, race and other covariates. These dose–response associations were observed in those with and without coexisting MS. The relative risks (95% CI) for CHF in those who had MS with serum 25(OH)D levels of < 18, 18–24 or 25–31 ng/mL compared with those with serum 25(OH)D ≥ 32 ng/mL were 2.45 (1.31–4.49), 2.04 (1.21–3.47) and 1.61 (0.91–2.83), respectively; in those who did not have MS, the risks were 1.61 (1.15–2.19), 1.39 (0.97–1.99) and 1.07 (0.77–1.49), respectively.

## DISCUSSION

The significant findings of the present study are that the elderly with lower diet folate and vitamin $B_{12}$ intake, lower serum vitamin D concentration and elevated serum inflammatory biomarker levels are likely to have a higher prevalence of CHF. The association remained statistically significant after adjustment for several known CHF factors and this association was even greater in subjects with coexisting MS.

Congestive heart failure is chiefly the end stage of hypertensive, coronary and valvular cardiovascular disease. Primary myocardial disease can also lead to CHF. There is no doubt that controlling these diseases is important in preventing and attenuating the development of CHF.[1,2,4,9] Furthermore, there is increasing evidence that micronutrients may play an important role in the pathogenesis of CHF.[3,10,11] Four major potential mechanisms may be important in explaining the protective effects of micronutrients against CHF, as follows.

1. Folate and vitamin $B_{12}$ are involved the regulation of homocysteine metabolism. Vitamin D downregulates nuclear factor-κB activity, increases interleukin (IL)-10 production and decreases IL-6, IL-12, interferon-γ and tumour necrosis factor-α production, leading to a cytokine profile that favours less inflammation.
2. Vitamin D is known to be a negative endocrine regulator of the renin–angiotensin–aldosterone system, which has a considerable impact on the regulation of blood pressure.
3. Vitamin D affects myocardial cell hypertrophy and proliferation, because cardiac muscle cells possess vitamin D receptors and calcitriol-dependent $Ca^{2+}$ binding proteins.
4. Serum 25(OH)D is a major factor that determines the circulating levels of parathyroid hormone (PTH). An inverse association of serum 25(OH)D and calcitriol (the active form of vitamin D) concentrations with PTH levels has been observed in healthy adults and CHF patients. Excess PTH levels are known to increase blood pressure and cardiac contractility, leading to cardiomyocyte hypertrophy.[12–14]

It should be noted that socioeconomic factors (including health policy) also strongly affect nutrition status in the elderly, which is beyond the scope of the present paper.

In conclusion, although a cause–effect association could be not interpreted in the present study owing to the nature of the cross-sectional study design, the results do extend our knowledge of micronutrients in relation to the risk of CHF and support that improving micronutrient status may play an important role in primary prevention of CHF and may further attenuate the progression of CHF development in the elderly with CHF.

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## CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

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