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Nutritional intake and oxidative stress in chronic heart failure

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Abstract *Background and aims:* Patients with chronic heart failure (CHF) are known to be at risk of malnutrition, and cardiac cachexia is an adverse prognostic indicator. The aim of this study was to determine the dietary adequacy of CHF patients compared with Dietary Reference Values, to compare the nutritional intake and status of CHF patients to a healthy comparison group, and finally to determine whether nutritional intake and status depended on New York Heart Association (NYHA) functional class.

Methods and Results: Patients with CHF ($n = 39$) and a comparison group of 27 healthy participants, who did not have CHF, were asked to complete a four-day food diary, and energy and nutrient intakes were calculated. F_{2_{ox}}-isoprostanes were measured in urine as an indicator of oxidative stress and antioxidants were measured in serum or plasma. Overall 73% of the CHF patients were consuming less than recommended energy intakes, and more than 50% of these patients were also consuming less than recommended vitamin D, selenium and zinc intakes. Nutrient intake (energy, vitamin B6, D, E, iron, folate and riboflavin) was lower in CHF patients than in the comparison group, with vitamin B6 and folate intake and antioxidant status decreasing, and isoprostane status increasing as NYHA functional class increased.

Conclusion: The majority of CHF patients do not meet dietary reference values for energy and a range of nutrients, and nutrient intake is lower in CHF patients than in healthy individuals. Dietary inadequacy tends to be increased in those with more severe disease.

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Introduction

Between 35 and 53% of patients with chronic heart failure (CHF) suffer from some form of malnutrition [1–3] and cardiac cachexia is a strong independent risk factor for mortality in such patients [4]. Several mechanisms may play a role in the development of malnutrition and cachexia in patients with CHF [5–9]. Micronutrient deficiency may be the cause as well as the consequence of CHF [10,11]. Despite the relevance of this area, there are few published data on dietary intake in patients with CHF [12,13], and most assessments of patient appetite are made from retrospective quality-of-life questionnaires. In this study, we have compared nutrient intake from a group of CHF patients to recommended intakes. As recommended intake levels are not always met, even by the general population, and because no recommended levels exist for many biochemical indicators of nutritional status, including lipid-soluble and other antioxidants, we have also compared nutrient intake and biomarkers of oxidative stress and antioxidant status with a healthy volunteer comparison group. Finally, we have examined how nutritional intake and antioxidant and oxidative stress status varies by New York Heart Association (NYHA) functional class, which is an indication of symptom/disease severity.

Methods

Patients with CHF were recruited from clinics in the Royal Victoria Hospital and Mater Hospital, Belfast from January 2003 until June 2004. All patients had a clinical diagnosis of CHF, as defined by the European Society of Cardiology guidelines [14], and were patients with stable symptoms on optimal medical therapy as tolerated by the individual patient. A group of comparison participants was also recruited through posters inviting hospital visitors and staff and members of voluntary organizations to participate. Comparison group participants were excluded if they had any history of CHF. Patients and comparison group participants were excluded if they had any of the following exclusion criteria: recent myocardial infarction or percutaneous coronary intervention, history of significant alcohol ingestion (>40 units per week), severe renal or hepatic dysfunction, or uncontrolled diabetes mellitus. Demographic information and details of current medication were collected for each participant.

All participants had an echocardiogram and underwent cardiopulmonary exercise testing (CPEX) to provide an objective assessment of their exercise capacity [15]. Stage of heart failure was assessed according to the New York Heart Association (NYHA) functional classification system. All CHF patients were asked to complete a Quality of Life questionnaire [16]. Venous blood samples were taken from all participants for the measurement of N-terminal pro B-type natriuretic peptide (NT-proBNP), measured on a Cobas e-module analyser (Roche Diagnostics, Burgess Hill, UK) [17]. Carotenoids were measured in serum by HPLC with diode array detection [18], and plasma vitamin C by enzymatic oxidation [19]. Participants also provided a urine sample for measurement of $F_{2\alpha}$ -isoprostane levels by gas chromatography-mass spectrometry (GC-MS) [20,21].

All participants were asked to complete a four-day food diary to assess usual dietary intake. Diaries were given to the participants at the introductory visit, and contained detailed written instructions on how to complete the diary, including a completed sample page. Detailed verbal instructions were also given by one of the investigators (CH) on how to complete the diary. Participants were requested to give information on type and quantity of all food eaten, and were asked not to make any alteration to their usual diet for the duration of the period. Diaries were completed prospectively over a four-day period, which consisted of three week days and one weekend day in order to represent changes in eating pattern over a complete week. Participants were requested to complete the diary during a four-day period immediately prior to their baseline visit in order to aid recall during the baseline visit. The diaries were reviewed with the patient to ensure accuracy and completeness. Portion sizes were calculated using a standard food atlas, patient measurement or manufacturer information. Energy and nutrient intakes were calculated by entering the dietary data onto an extensive computerised food analysis database based on UK food composition tables (WISP, Tinuviel Software, Warrington, U.K.), and compared to UK Department of Health Dietary Reference Values (DRVs) [22].

Statistical analysis was performed using SPSS statistical software package (SPSS Inc., Chicago). Independent samples *t* tests and one way analysis of variance (followed by the Newman–Keuls multiple-range comparison test) were used to compare normally distributed data, which were then expressed as mean (standard deviation (SD)). Data were logarithmically transformed where necessary, and data then presented as geometric mean (interquartile range).

Written informed consent was obtained from each participant. The study was approved by the Research Ethics Committee of Queen's University Belfast and the investigation conformed with the principles outlined in the Declaration of Helsinki.

Results

There were sixty-seven participants enrolled in this study. One patient died after enrolment prior to the baseline visit and any data being obtained. The remaining sixty-six participants included 39 CHF patients (6 female and 33 male) and 27 comparison group participants (6 female and 21 male). Of the 39 CHF patients, 18 had NYHA class II heart failure symptoms, 15 were in NYHA class III and 6 were in NYHA class IV. Due to the small numbers of patients who were NYHA class IV, a combined NYHA class III and IV group was created ($n = 21$). The aetiology of CHF was ischaemic heart disease in 32 patients, idiopathic dilated cardiomyopathy in 5 patients and valvular heart disease in 2 patients. A summary of CHF patient characteristics compared to comparison group participants is shown in Table 1.

Peak achieved oxygen uptake capacity was reduced in patients (12.4 vs 20.0 ml/min/kg, $P = 0.016$). Scores on the Minnesota Quality of Life questionnaire ranged from 5 to 99 out of a possible maximum score of 105 (mean 44.4). Levels of

Table 1 Demographic and clinical characteristics of the CHF patients and comparison group participants.

	CHF (n = 39)	Comparison group (n = 27)	P
Age (years)	66 ± 10	60 ± 10	0.019
Body mass index (kg/m ²)	27.6 ± 3.2	27.4 ± 5.7	0.88
Current smoker	7 (18%)	3 (11%)	<0.001
Ex smoker	23 (59%)	6 (22%)	0.001
Never smoked	9 (23%)	18 (67%)	<0.001
Mean Pack years	57 ± 43	39 ± 27	0.24
Diabetes	12 (31%)	2 (7%)	0.02
Hypertension	13 (33%)	8 (30%)	0.76
Hypercholesterolaemia	17 (44%)	7 (26%)	0.18
Fluid restriction	17 (44%)	– (0%)	<0.001
Salt restriction	15 (38%)	2 (7%)	<0.001
Vitamin supplement	8 (21%)	12 (44%)	0.04
Dietary supplement	8 (21%)	8 (30%)	0.2
Dietary restriction	22 (56%)	5 (19%)	<0.001
History of IHD	32 (82%)	1 (4%)	<0.001
Previous MI	23 (59%)	– (0%)	<0.001
CABG	12 (31%)	– (0%)	0.001
ACE Inhibitor/ARB	33 (85%)	6 (22%)	<0.001
Beta-blocker	31 (79%)	1 (4%)	<0.001
Aspirin	15 (38%)	5 (19%)	0.06
Diuretic (loop/thiazide)	30 (77%)	4 (15%)	<0.001
Digoxin	18 (46%)	1 (4%)	<0.001
Spirolactone	21 (54%)	– (0%)	<0.001
Warfarin	16 (41%)	– (0%)	<0.001
Statin	26 (67%)	2 (7%)	<0.001

IHD – ischaemic heart disease; MI – myocardial infarction; CABG - coronary artery bypass grafting; ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker.

Dietary restriction – participants reported they had been advised to follow a low fat, low salt or diabetic diet or combination of these. Dietary supplement includes over the counters supplements such as cod liver oil capsules, garlic capsules, evening primrose oil capsules and herbal supplements.

NT-proBNP were higher in CHF patients than in the comparison group (1333 (725, 3025) ng/ml vs 38 (20, 95) ng/ml, $P = <0.001$), therefore confirming the presence of CHF.

Completed food diaries were returned by 37 of the 39 CHF patients and all 27 of the comparison group participants. Nutrient intake data were compared to DRVs [22] for energy, macronutrients and micronutrients in CHF patients and the percentage of the population consuming less than the DRVs is presented in Table 2. Energy intakes were compared to age- and gender-specific DRVs. Overall, 73% of the CHF population was consuming less than the Estimated Average Requirements. Protein intake was less than the Reference Nutrient Intake (RNI) for 19% of CHF patients, whilst fat consumption was close to population average, with only 22% and 16% of the population falling under the DRVs for total and saturated fat respectively. Total carbohydrate intake was below the DRV in 62% of the CHF patients.

In terms of micronutrient intake, more than 50% of the CHF population consumed less than the RNIs for vitamin D (97% of population), zinc (65%) and selenium (95%), whilst 46% of CHF patients consumed less than the recommended values of iron and folate.

Nutrient intake in the CHF patients (according to NYHA functional class) and the comparison group is shown in Table 3. Energy intake was lower in CHF patients compared

to the comparison group, but energy intake did not differ by NYHA functional class. Carbohydrate and total fat intake were also lower in CHF patients than in the comparison group, but this largely disappeared when adjusted for energy intake. Vitamin B6, D, E, iron, folate and riboflavin intake were all significantly lower in CHF patients than in the comparison group, with vitamin B6 and folate intake also decreasing as NYHA functional class increased.

Antioxidant status by NYHA class is shown in Table 4. There were significant differences in concentrations of lutein, zeaxanthin, β -cryptoxanthin and α -carotene between the comparison group, NYHA class II patients and NYHA class III and IV patients, with a decrease in concentration as NYHA functional class increased.

Concentrations of isoprostanes in CHF patients and the comparison group are also shown in Table 4. Isoprostanes were significantly higher in NYHA class III and IV than in the comparison group or NYHA class II group.

Discussion

Our study shows that 73% of CHF patients did not achieve recommended energy levels for their age and gender. More than 40% of CHF patients also had lower than recommended intakes of carbohydrate, vitamin D, selenium, zinc, iron and folate. Nutrient intake (energy, vitamin B6, D, E, iron,

Table 2 Percentage of CHF patients not meeting Dietary Reference Values (DRV).

Nutrient	DRV	% of population (CHF patients) consuming less than DRV (n = 37)
Energy	19–50 y Male 2550; Female 1940 kcal/d	50
	51–59 y Male 2550; Female 1900 kcal/d	83
	60–64 y Male 2380; Female 1900 kcal/d	50
	65–74 y Male 2330; Female 1900 kcal/d	92
	75+ y Male 2100; Female 1810 kcal/d	91
	Average (mean)	73
Protein	Male 53.3; Female 46.5 g/d	19
Total fat	33 (% of total energy)	22
Carbohydrate	47 (% of total energy)	62
Saturated fat	10 (% of total energy)	16
Vitamin C	40 mg/d	32
Vitamin D	10 mg/d	97
Vitamin E	Male 4; Female 3 mg/d	24
Thiamin	Male 0.9; Female 0.8 mg/d	14
Riboflavin	Male 1.3; Female 1.1 mg/d	35
Vitamin B6	Male 1.4; Female 1.2 mg/d	30
Iron	8.7 mg/d	46
Folate	200 µg/d	46
Zinc	Male 9.5; Female 7 mg/d	65
Selenium	Male 75; Female 60 µg/d	95
Vitamin B ₁₂	1.5 µg/d	3
Sodium	1600 mg/d	14

folate and riboflavin) was lower in CHF patients than in the comparison group. Vitamin B6 and folate intake, and antioxidant status also decreased, while isoprostanes increased as NYHA functional class increased.

There are few published data on nutritional intake in CHF patients. This may in part be due to the difficulty in obtaining this information. Assessment of dietary intake is time-consuming and labour-intensive, and requires a high

Table 3 Nutrient intake in CHF patients (classified according to NYHA functional class) and comparison group.

Nutrient	Units	Comparison group (n = 27)	CHF patients		p-value
			NYHA II (n = 18)	NYHA III and IV (n = 19)	
Energy	kcal	2275 (508) ^a	1790 (438) ^b	1794 (685) ^b	0.004
Protein	g	91.6 (25.5)	74.5 (21.9)	77.3 (35.4)	0.09
	% of total energy	16.1 (2.4)	16.7 (2.7)	17.3 (3.8)	0.42
Total fat	g	97.5 (31.7)	74.5 (18.4)	80.7 (40.6)	0.05
	% of total energy	38.1 (5.4)	37.9 (6.5)	39.4 (6.0)	0.69
Carbohydrate	g	244.7 (45.0) ^a	196.7 (61.9) ^b	191.7 (58.6) ^b	0.002
	% of total energy	43.7 (6.4)	43.9 (6.7)	44.3 (6.8)	0.96
Saturated fat	g	36.7 (15.6)	27.5 (7.9)	29.7 (18.2)	0.10
	% of total energy	14.2 (3.5)	14.1 (3.8)	14.7 (5.2)	0.92
Vitamin C [#]	mg	85.3 (47.0, 137.0)	62.7 (34.5, 95.5)	51.9 (30.0, 113.0)	0.10
Vitamin D [#]	µg	3.41 (2.58, 5.31)	2.16 (1.63, 3.23)	1.80 (0.88, 3.42)	0.05
Vitamin E [#]	mg	9.61 (7.18, 11.63) ^a	5.71 (3.89, 9.93) ^b	5.93 (3.83, 9.88) ^b	0.01
Thiamin	mg	1.67 (0.44)	1.45 (0.45)	1.40 (0.53)	0.11
Riboflavin	mg	1.89 (0.70) ^a	1.40 (0.56) ^{a,b}	1.51 (0.80) ^{a,b}	0.05
Vitamin B6	mg	2.58 (0.86) ^a	2.04 (1.00) ^{a,b}	1.86 (0.85) ^b	0.02
Iron	mg	13.6 (4.1) ^a	10.3 (4.5) ^b	9.0 (3.4) ^b	0.001
Folate	µg	273.4 (103.7) ^a	232.0 (86.9) ^{a,b}	211.4 (80.9) ^b	0.04
Zinc	mg	10.4 (3.8)	8.5 (3.3)	8.9 (4.5)	0.21
Selenium	µg	48.0 (17.6)	40.4 (17.4)	43.0 (22.8)	0.41
Vitamin B ₁₂ [#]	µg	5.25 (3.46, 6.85)	4.06 (2.87, 5.88)	3.80 (2.56, 6.28)	0.15
Sodium	mg	3118 (957)	2985 (731)	2950 (1357)	0.84

Nutrient intake was compared between groups by one way analysis of variance. Superscripted letters indicate homogeneous subsets (Student-Neuman-Keuls multiple-range test). Data presented as mean (standard deviation) except for [#]where data presented as geometric mean (interquartile range).

Table 4 Antioxidant and isoprostane status in CHF patients (classified according to NYHA functional class) and comparison group.

	Comparison group (n = 27)	CHF patients		p-value
		NYHA II (n = 18)	NYHA III and IV (n = 21)	
Vitamin C (μmol/l)	57.2 (18.1)	43.3 (22.2)	46.8 (25.5)	0.09
Lutein (μmol/l)	0.145 (0.048)	0.133 (0.050)	0.091 (0.035)	<0.001
Zeaxanthin (μmol/l)	0.032 (0.012) ^a	0.029 (0.013) ^a	0.019 (0.010) ^b	0.001
β-cryptoxanthin (μmol/l) [#]	0.067 (0.043, 0.103) ^a	0.052 (0.033, 0.092) ^{a,b}	0.038 (0.022, 0.058) ^b	0.04
α-carotene (μmol/l) [#]	0.078 (0.044, 0.145) ^a	0.062 (0.033, 0.116) ^{a,b}	0.045 (0.024, 0.083) ^b	0.05
β-carotene (μmol/l) [#]	0.288 (0.201, 0.467)	0.197 (0.119, 0.316)	0.219 (0.120, 0.409)	0.17
Lycopene (μmol/l)	0.678 (0.341) ^{a,b}	0.397 (0.354) ^b	0.549 (0.436) ^b	0.06
Isoprostanes (ng/mg creatinine)	0.082 (0.053, 0.095) ^a	0.104 (0.063, 0.171) ^a	0.449 (0.173, 0.698) ^b	<0.001

Antioxidant and isoprostane status was compared between groups by one way analysis of variance. Superscripted letters indicate homogeneous subsets (Student-Neuman-Keuls multiple-range test). Data presented as mean (standard deviation) except for [#]where data presented as geometric mean (interquartile range).

degree of patient co-operation. Our results are similar to a previous study [12], which reported negative nitrogen and energy balance in the CHF group, although micronutrient intake was not measured. Negative nitrogen balance is suggestive of a hypermetabolic state and would support previous studies suggesting increased resting energy expenditure in CHF patients [4,23]. In another study of elderly patients with CHF (mean age 80.8 yr), 25 of the 39 patients (64%) studied had energy intakes below their estimated requirements, with many also failing to achieve their recommended intakes of carbohydrate and fat [13].

The possible reasons for reduced food intake in patients with CHF are complex and multifactorial. In another study, using a Food Eating Experiences and Diet (FEED) questionnaire designed to assess factors affecting hunger and appetite, patients rated their hunger and appetite and the extent to which different factors associated with hunger and appetite affected their food intake on a Likert-type scale [3]. The results from this study suggest that dietary restriction, reduced hunger sensation, fatigue, shortness of breath, nausea, anxiety, and low mood all contribute to reduced food intake. Many of these factors were not reported in the healthy elderly control group.

Many of the CHF patients in our study had been instructed to follow a low salt, low fat or combination diet. At least 56% of the CHF patients reported some type of dietary restriction. There was a higher prevalence of diabetic patients within the CHF group (31% compared with 7% of comparison group), and again these patients had been advised about dietary restrictions. A perceived restriction in the variety of food available may affect appetite in some patients or lead to a very unvaried diet. However, our study did not look at the factors responsible for dietary choices and food intake. It is interesting, however, that only 38% of CHF patients were aware that they should be on a low salt diet, and the majority (86%) of patients were exceeding the DRV for salt. The majority of CHF patients also exceeded DRVs for total and saturated fat despite many stating that they were on a low fat diet.

Our study and previous work [13] have indicated low vitamin D intake in CHF patients, and this is likely to be compounded by immobility and lack of sunlight exposure, leading to an overall low vitamin D status. Vitamin D is one of

the few micronutrients examined using intervention trial methodology in CHF. In a randomised controlled trial of the effect of supplementation with 50 μg vitamin D3 plus 500 mg calcium or placebo and 500 mg calcium daily, there was a significant improvement in vitamin D status and cytokine profile [24], but no significant difference in survival rates was found between the groups, possibly because of the relatively short duration of the study and the fact that patients were at a late stage in the disease [25].

There is evidence of oxidative stress in patients with CHF [26,27]. Isoprostanes are a reliable, reproducible and sensitive marker of such stress *in vivo* [28]. Increased levels of urinary isoprostanes have previously been described in patients with CHF [29,30]. We were able to relate increasing levels of isoprostanes and reduced antioxidant concentrations to increasing NYHA functional class. In a previous study, multiple micronutrient supplementation, including the antioxidant vitamins C and E, improved left ventricular function and quality-of-life scores in a small group of elderly patients with CHF [31]. In contrast, antioxidant supplementation with vitamin E (α-tocopherol) alone did not help patients with CHF [32] and may even be harmful [33]. More studies are needed before routine antioxidant treatment can be recommended for patients with CHF.

Malnutrition, inflammation, and oxidative stress may interact to influence the wasting and cachexia that are independent predictors of increased mortality in CHF [4,34]. Therefore our observation that oxidative stress and low energy intake increase as NYHA functional class increases highlights the potential importance of nutritional strategies to combat this malnutrition-inflammation-cachexia (MIC) syndrome. The fact that obesity has been associated with improved survival in CHF, the so-called "reverse epidemiology" phenomenon [35], also points to the potential for nutritional strategies to be used in CHF to maintain dietary adequacy and improve survival.

Limitations of the study

The number of CHF patients in this study is small and reflects the difficulty in recruiting patients with CHF for this type of research. With such numbers, it is not possible to

correlate measurements with events, such as hospital admissions or mortality. There was a small but significant difference in age between the two study groups, with CHF patients having a higher mean age than comparison group participants. Many of the comparison group individuals were workers on the site, therefore biasing the comparison group towards a younger group of people within the working age range.

In studies of dietary intake, there is evidence of considerable under-reporting of food intake using questionnaires [36,37]. In our study, all patients had the food diary explained to them by the investigator at their introductory visit, and were given detailed instructions how to fill it in. Participants were asked whenever possible to weigh food or to bring food packaging with them to the study visit. Some of the participants were taking commercially available vitamin supplements, but we did not include micronutrient intake from supplements in the analysis of dietary micronutrient intakes, and therefore the micronutrient intakes reported are from food alone.

In summary, our study shows that the majority of CHF patients do not meet dietary reference values for energy and a range of nutrients, and that nutrient intake was lower than a comparison group of healthy individuals. There was also some evidence of dietary inadequacy being increased in those with more severe symptoms. In light of the prevalence of CHF and the associated morbidity and mortality, dietary adequacy, and nutritional strategies to promote dietary adequacy, are important areas for further research.

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