Intentional Weight Loss Improved Performance in Obese Ischaemic Heart Patients: A Two Centre Intervention Trial

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Abstract

Aims: The risk of heart failure (HF) increases with BMI, but paradoxically obesity has been associated with reduced mortality in patients with HF. The effect of intentional or therapeutic weight loss on HF is not well known. We examined the effect of weight loss induced by low energy diet (LED) on physical performance and cardiovascular risk factors in obese patients with moderate-to-severe HF or ischaemic heart disease (IHD).

Methods and Results: Results from two weight loss interventions at two centres, one in Denmark (DK - 12 week intervention in 21 subjects (14 LED, 7 controls)) and one in UK (16 week intervention in 11 subjects (all LED, no controls) were combined for a total of 32 subjects with HF or IHD and median BMI 36.2 kg/m2 (range 30-50). Weight loss was initiated with LED (800 kcal/day) followed by energy restricted and protein-rich diet (1200 kcal/day). Physical performance was measured by six-minute walk test (DK) and maximum oxygen uptake (UK). The effect of treatment was analysed using linear mixed model. Weight loss in the intervention group: 13.9 kg ± 6.5 and 1.21 kg ± 1.8 in controls (P=0.000). Physical performance (the primary outcome) was improved by 17.8% ± 23.1 in the intervention group versus -22.1% ± 25.6 in the control group (P=0.000). Treatment also improved triglycerides (P=0.000), very low lipoprotein (P=0.001) and C-reactive protein (P=0.010).

Conclusion: Weight loss induced by LED in obese patients with moderate-to-severe HF or IHD resulted in clinically significant improvement in physical performance and cardiovascular risk markers.

Keywords: Heart Failure; Ischaemic Heart Disease; Weight Loss; Maximum Oxygen Uptake; Six Minutes Walk Test
Introduction

Obesity is an important risk factor for the development of cardiovascular disease, including the development of heart failure (HF) [1]. The risk of developing HF increases both with the severity of obesity (in the Framingham Heart Study the risk of HF increased by 7% in women and 5% in men for each 1 kg/m² increment in BMI [2]) and its duration [3]. Despite this strong association between obesity and HF, several studies have found that lower body weight predicts increased mortality in people with diagnosed HF [4]. A meta-analysis of the relationship between body mass index (BMI) and mortality in patients with HF found that overweight and obesity were associated with lower all-cause and cardiovascular mortality [5]. Classifying by BMI class revealed a U-shaped relationship, with lowest risk of mortality at BMI 25-35 kg/m² [6]. In a systematic review and meta-analysis including 2.88 million individuals Flegal et al. found a J-shaped relation between BMI and all-cause mortality [7]. The lowest all-cause mortality was at BMI 25-30 kg/m². Relative to normal weight, obesity was associated with significantly higher all-cause mortality [7]. Kapoor and Heidenreich found the lowest risk of mortality in 542 obese HF patients over 60 years of age was at BMI 36-40 kg/m² [8]. In contrast a study in nearly 8000 subjects with chronic mild to moderate HF and diabetes mellitus (DM) found that obesity conferred no survival benefit [9]. The studies linking low weight to mortality have all been observational and their design, in particular their failure or inability to differentiate between the effect of intentional and unintentional low weight, undermines their validity [10,11]. We hypothesized that intentional weight loss would improve the physical performance of obese patients with HF or ischaemic heart disease (IHD). This was investigated at two centres, one in Denmark (DK) and one in Britain (UK). Both studies were performed as pilot studies to assess the feasibility, safety and size of effects of therapeutic weight loss induced by low energy diet (LED) in obese patients with moderate-to-severe HF or IHD. The primary outcome at both centres was change in physical performance, measured in the form of six-minute walk test (6-MWT) at the Danish centre and in the form of cardiac performance measured by maximum oxygen uptake (VO2max) at the UK centre. Changes in 6-MWT predict the changes in VO2max and survival in patients with severe HF [12,13]. Secondary outcomes were feasibility and safety of LED induced weight loss, and changes in metabolic parameters.

Methods and Materials

Two trials were undertaken: one at The Copenhagen University Hospital, Gentofte, Denmark (DK centre), and one at the Cambridge University Hospitals NHS Trust, UK (UK centre). The trials were comparable in design, subjects, method and duration (Table S1 in supplemental material). All subjects were diagnosed with moderate to severe HF or IHD and all but one in each randomization had one or more co-morbidities (Table S2 in supplemental material). Inclusion and exclusion criteria are shown in Table 1. The investigations conform to the principles outlined in the Declaration of Helsinki.

### Table 1. Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>DK centre</th>
<th>UK centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>BMI ≥ 30 - 50 kg/m²</td>
<td></td>
</tr>
<tr>
<td>Age 25-70 years</td>
<td>Age 25-70 years</td>
<td></td>
</tr>
<tr>
<td>Diagnosed heart failure</td>
<td>Stable heart failure NYHA class II or III OR subjects with one NYHA class II or III of additional cardiovascular risks</td>
<td></td>
</tr>
<tr>
<td>Obtained informed consent</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes or pre-diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of IHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obtained informed consent</td>
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</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>DK centre</th>
<th>UK centre</th>
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<tbody>
<tr>
<td>Unable to complete 6-MWT</td>
<td>≥ 5% recent weight loss</td>
<td></td>
</tr>
<tr>
<td>≥ 10% weight loss 6 months prior study start</td>
<td>Changed heart failure medication 6 weeks prior to study</td>
<td></td>
</tr>
<tr>
<td>Recent pharmacologic change</td>
<td>Planned therapeutic changes during the study period</td>
<td></td>
</tr>
<tr>
<td>Planned therapeutic changes during the study period</td>
<td>Peripheral vascular disease of a degree to prohibit undertaking exercise test</td>
<td></td>
</tr>
<tr>
<td>Recent unstable angina</td>
<td>Acute myocardial infarction or unstable angina within 3 months prior to study</td>
<td></td>
</tr>
<tr>
<td>Pregnancy (actual or planned)</td>
<td>Uncontrolled arrhythmias causing symptoms or haemodynamic compromise (systolic BP &lt;90 mmHg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any significant valvular heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequately controlled hypertension defined by resting BP &gt; 170/95 mmHg</td>
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</tbody>
</table>

Statistical analyses were performed to investigate the comparability of data from the two centres, and between HF and non-HF patients (Table S3, S4, S5 and S6 in supplemental material). T-test of baseline data showed subjects in DK were older (P=0.044), and had lower fat mass (FM) (P=0.000) and tumour necrosis factor alpha (TNF-α) (P=0.000), and higher insulin (P=0.037) and fat free mass (FFM) (P=0.017). T-test of baseline data from HF and non-HF patients showed that HF patients had lower percentage of FM (P=0.002), higher FFM (P=0.030), and lower TNF-α (P=0.027). To take into account the differences in baseline values the statistical analyses were adjusted for these. Data from the two centres are combined in all the statistical analyses, and in all tables and figures in the article, unless otherwise stated. The two trial outlines and flowcharts are presented in Figures 1 and Figure S1 (supplemental material). Methods and materials for the two trials are described separately.

Subjects – UK centre

Subjects were identified from patient records at Addenbrooke’s Hospital, Cambridge, UK. Recruitment was extended to general practitioners, and cardiology departments at Luton and Dunstable, Bedford, and West Suffolk Hospitals, UK. A total of 34 individuals were screened, 14 met the inclusion criteria and were included in the study. Three dropped out, one due to cancer, one was intolerant to the diet, and one was allocated to control (group subsequently terminated due to insufficient number of subjects). A total of 11 subjects completed the intervention, four had moderate-to-severe HF, NYHA II or III; the remaining subjects had major cardiovascular risk factors (Table S1 in supplemental material).

Diet – DK centre

All subjects were advised to adhere to dietary advice according to the European Society of Cardiology [14]. The diet during week 0 through 8 (Table 2) provided the intervention subjects with BMI below 40 kg/m² with 800 kcal/day, and subjects with BMI above 40 kg/m² with 1000 kcal/day. The diet was a mainly liquid LED of 6 sachets Nupo®, and one Nupo® snack bar or 200g of specified vegetables, daily (Nupo®, Denmark). Six sachets (equivalent to ≈750 kcal) of the LED products supplied subjects with the recommended daily amount of vitamins and minerals. At the baseline visit the intervention group received a package containing all the various flavours of Nupo® shakes and soups. At the following interim visits through week six the subjects were supplied with the product flavours they preferred, e.g. one subject chose only soup and another chose only two different flavours of shakes. From week eight through 12 the intervention group followed plan of energy restricted reintroduction to regular foods supplying 1200 kcal/day. The diet included two daily Nupo® LED products (one sachet and one meal replacement bar) in combination with regular foods based on recipes with high amounts of protein and low amounts of carbohydrate. Control group subjects attended the same number of interim visits as the intervention group throughout the trial and were instructed to adhere to a conventional diet according to the Nordic Nutrition Recommen-
end of the trial by measuring 6-MWT - subjects walked six min-
ute(s) at a comfortable pace on a 30 meter long track in a base-
ment corridor. The 6-MWT serves as an indicator for exercise
tolerance and is validated to reflect change in cardiac capacity
and exertion in concordance with change in symptoms in HF
patients [13,16,17]. Information on background cardiovascular
risk factors including left ventricular ejection fraction and pharma-
cotherapy was retrieved from medical records.

Anthropometric measures and functional status –
UK centre

Height was measured to the nearest 0.5 cm using a wall-mount-
ed stadiometer (Seca, Hamburg, Germany) at baseline. Anthro-
pometric measures were obtained at baseline, week six and
week sixteen. Body composition, FM and FFM were measured
using a four-component model described elsewhere [18]. VO2-
max served as an indicator of cardiac performance and was
assessed by cardiopulmonary exercise testing.

Diet – UK centre

Subjects consumed a milk-based LED for the first six weeks
of the trial, followed by 10 weeks energy restricted reintroduc-
tion to regular foods (Table 3). The LED was based on semi-
skimmed milk, providing 800 kcal (2.4 L milk) per day for sub-
jects with BMI below 40 kg/m2, and 1000 kcal (3 L milk) per
day for subjects with a higher BMI. Patients were instructed to
consume 2-2.5 gram of sodium in the form of either Bovril® or
stock cubes. In addition one to two sachet of Fybogel® (‘Isp-
aghula husk’), and a mineral and vitamin supplement (two
Sanatogen gold® tablets, Bayer plc, Berkshire, UK), were con-
sumed daily. An alternative diet using commercially available
products (e.g., Slim Fast®, Surrey, UK) was provided for sub-
jects who found ‘simple milk’ unpalatable. Subjects followed
an individual energy restricted reintroduction to regular foods
supplying approximately 1400 kcal per day through weeks
6-16 supplying subjects with 80% of estimated energy needs.
A daily dose of Orlistat (Xenical®, Roche Welwyn Garden City,
UK) 120 mg tablets was prescribed in order to further aid
weight loss maintenance during the second phase.

Anthropometric measures and functional status –
DK centre

Anthropometric data were collected at all visits prior to giving
dietary advice. Height was measured at baseline to nearest 0.5
cm using a wall-mounted stadiometer (Seca, Hamburg Ger-
many). Subjects, wearing only undergarments and without shoes,
were weighed to nearest 0.1 kg using a calibrated professional
scale (Tanita HD-351, Tanita Corporation of America, Illinois,
USA). Body composition was estimated by bioelectric imped-
ance (Tanita BC-418, Tanita Corporation of America, Illinois,
USA). Physical performance was assessed at baseline and the
end of the trial by measuring 6-MWT - subjects walked six min-
utes [15].

Table 2. Composition of energy percentage of the diets during the study period.

<table>
<thead>
<tr>
<th></th>
<th>LED</th>
<th>Reintroduction</th>
<th>Control</th>
<th>Conventional*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DK centre</td>
<td>UK centre</td>
<td>DK centre</td>
<td>UK centre</td>
</tr>
<tr>
<td>Energy, kcal per day</td>
<td>800-1000</td>
<td>800-1000</td>
<td>1200</td>
<td>1400*</td>
</tr>
<tr>
<td>Protein, E%</td>
<td>35-40</td>
<td>43</td>
<td>30-35</td>
<td>-</td>
</tr>
<tr>
<td>Fat, E%</td>
<td>20-25</td>
<td>3</td>
<td>20-25</td>
<td>-</td>
</tr>
</tbody>
</table>
| Of which satu-
| rated, E%       | 4                  | - Max 10           | - Max 10           | -                  |
| Carbohydrate, E%| 35-40              | 50                 | 40-45              | -                  | 50-60              |
| Dietary fibre, g per day | 25                 | 3.5-7              | 25-35              | -                  | 25-35              |

*Dietary advice based on the Nordic Nutrition Recommendations 2004 (Becker, 2005); *equivalent
to approximately 80% of the individual needs; E%: energy percentage; LED: low energy diet.
Blood analysis – UK centre

Venous blood was drawn in the fasting state at weeks 0, 6 and 16, and plasma was immediately obtained and stored at -20°C. Routine biochemical analyses were performed after every visit to quantify plasma glucose, TG, total cholesterol, and HDL. All other biochemical analyses were performed in one batch. Both VLDL and LDL were calculated from Friedewald’s formula. CRP was measured by using high-sensitivity, two-site enzyme linked immunoassay (ELISA) as described elsewhere [19]. Adiponectin and leptin were assayed by two-site microtitre plate-based DELFIA (Perkin Elmer Life Sciences, Wallac Oy, Turku, Finland). Antibodies and standards reagents were supplied by R&D Systems (R&D Systems Europe, Abingdon, UK). Between batch CVs for adiponectin were 5.4% at 3.6 μg/mL, 5.2% at 9.2 μg/mL, and 5.0% at 15.5 μg/mL. Between batch CVs for leptin were 7.1% at 2.7 ng/mL, 3.9% at 14.9 ng/mL, and 5.7% at 54.9 ng/mL. Insulin was assayed in singleton on a 1235 Auto DELFIA (Perkin Elmer Life Sciences, Wallac Oy, Turku, Finland) automatic immunoassay system using a two-step time resolved fluorometric assay (Kit No. B080-101). Between batch CVs were 3.1% at 29 pmol/L, 2.1% at 79.4 pmol/L, 1.9% at 277 pmol/L, and 2.0% at 705 pmol/L. Plasma BNP concentration was assessed by Triage® BNP test kid (Biosite® Incorporated, California). TNF-α was assayed by quantitative ELISA technique with the reagent supplied by R&D Systems (R&D Systems Europe) and between batch CVs were 7% at 5.97 pg/mL, 2.5% at 8.3% at 37.4 pg/mL, 6.4% at 282 pg/mL, and 6.3% at 3869 pg/mL.

Statistics

The intervention group in the DK centre (N=14) and the UK centre are presented in Tables S7 and S8 in supplemental material. Data from a total of 25 patients were included in the analyses, and data from all seven control subjects were included unless otherwise stated. As two different, but comparable, methods were used to assess body composition, differences in %FM and TNF-α. There was no difference between intervention and control groups at baseline in 6-MWT (465 (327-524) meter (N=14) vs. 416 (374-514) meter (N=7) (P=0.908)) (DK centre only). Results from the DK centre (only including the initial intervention subjects (N=11)) and the UK centre are presented in Tables S7 and S8 (in supplemental material).

Results

Baseline characteristics are presented in Table 3. The only differences found between groups were in %FM and TNF-α. Differences found between intervention and control groups were in %FM and TNF-α. Baseline data are presented as medians and inter quartile range (IQR). Routine biochemical analyses were performed after every visit to quantify plasma glucose, TG, total cholesterol, and HDL. All other biochemical analyses were performed in one batch. Both VLDL and LDL were calculated from Friedewald’s formula. CRP was measured by using high-sensitivity, two-site enzyme linked immunoassay (ELISA) as described elsewhere [19]. Adiponectin and leptin were assayed by two-site microtitre plate-based DELFIA (Perkin Elmer Life Sciences, Wallac Oy, Turku, Finland). Antibodies and standards reagents were supplied by R&D Systems (R&D Systems Europe, Abingdon, UK). Between batch CVs for adiponectin were 5.4% at 3.6 μg/mL, 5.2% at 9.2 μg/mL, and 5.0% at 15.5 μg/mL. Between batch CVs for leptin were 7.1% at 2.7 ng/mL, 3.9% at 14.9 ng/mL, and 5.7% at 54.9 ng/mL. Insulin was assayed in singleton on a 1235 Auto DELFIA (Perkin Elmer Life Sciences, Wallac Oy, Turku, Finland) automatic immunoassay system using a two-step time resolved fluorometric assay (Kit No. B080-101). Between batch CVs were 3.1% at 29 pmol/L, 2.1% at 79.4 pmol/L, 1.9% at 277 pmol/L, and 2.0% at 705 pmol/L. Plasma BNP concentration was assessed by Triage® BNP test kid (Biosite® Incorporated, California). TNF-α was assayed by quantitative ELISA technique with the reagent supplied by R&D Systems (R&D Systems Europe) and between batch CVs were 7% at 5.97 pg/mL, 2.5% at 8.3% at 37.4 pg/mL, 6.4% at 282 pg/mL, and 6.3% at 3869 pg/mL.

Statistics

The intervention group in the DK centre (N=14) and the UK centre are presented in Tables S7 and S8 as well as the percentage of change from baseline to end of study. Results of the linear mixed model analyses are presented as mean ± standard error (SE). Results are interpreted using a significance level of 0.05. All statistical analyses were performed using Microsoft Excel and SPSS 21.0 for Windows.

Results from the DK centre (only including the initial intervention subjects (N=11)) and the UK centre are presented in Table 3. Only differences found between groups were in %FM and TNF-α. Results from the DK centre (only including the initial intervention subjects (N=11)) and the UK centre are presented in Table 3.

Table 3. Baseline characteristics in intervention and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (49-67)</td>
<td>64 (62-69)</td>
<td>0.096</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.75 (1.69-1.79)</td>
<td>1.78 (1.76-1.80)</td>
<td>0.335</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>110.0 (98.2-135.6)</td>
<td>114.6 (100.0-138.5)</td>
<td>0.858</td>
</tr>
<tr>
<td>BMI (m2/kg)</td>
<td>36.5 (33-43.0)</td>
<td>36.2 (30-43.7)</td>
<td>0.423</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>43.6 (40.6-53.6)</td>
<td>39.3 (23.9-53.4)</td>
<td>0.101</td>
</tr>
<tr>
<td>FM (%)</td>
<td>40.9 (37.3-43.0)</td>
<td>34.3 (28.3-38.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>67.5 (59.6-77.5)</td>
<td>75.2 (67.3-84.6)</td>
<td>0.356</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.65 (1.25-2.22)</td>
<td>1.68 (1.22-2.88)</td>
<td>0.850</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.00 (3.00-4.65)</td>
<td>5.10 (3.90-5.70)</td>
<td>0.648</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.22 (1.70-3.06)</td>
<td>2.50 (1.90-4.00)</td>
<td>0.626</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.08 (0.91-1.33)</td>
<td>1.01 (0.91-1.31)</td>
<td>0.883</td>
</tr>
<tr>
<td>VLDL (mmol/L)</td>
<td>0.77 (0.50-1.00)</td>
<td>0.80 (0.50-1.30)</td>
<td>0.785</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.80 (5.70-8.30)</td>
<td>7.70 (6.60-8.10)</td>
<td>0.889</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>78 (55-109)</td>
<td>163 (49-253)</td>
<td>0.073</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>4.86 (1.63-11.3)</td>
<td>4.93 (2.20-16.2)</td>
<td>0.873</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>2.64 (1.84-4.03)</td>
<td>1.74 (1.73-1.89)</td>
<td>0.043</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>5.40 (3.32-7.83)</td>
<td>5.08 (4.25-10.49)</td>
<td>0.257</td>
</tr>
<tr>
<td>Leptin (pg/mL)</td>
<td>35.00 (24.83-50.79)</td>
<td>21.96 (12.56-48.59)</td>
<td>0.464</td>
</tr>
</tbody>
</table>

The use of LED improved the primary outcome, physical and cardiac performance, by 17.8% ± 23.1 from baseline to end of study in the intervention group, while physical performance decreased in the control group by 22.1% ± 25.6 (P=0.000) (Figure 2). 6-MWT increased by 20.4% ± 29.3 in the intervention group from baseline to end of study at the DK centre, and...
VO2max increased by 14.4% ± 12.0 in the intervention group at the UK centre.

All results from anthropometric and plasma variables are presented in Table 4. Body weight in the LED subjects was reduced by 13.9 kg ± 6.5 versus 1.2 ± 1.8 in the control group (P=0.000). The weight lost by LED consisted mostly of FM (68%), while almost none of the metabolized tissue in the control group was FM (<1%) (P=0.001).

Of the plasma lipids, triglyceride (TG) and very-low-density lipoprotein (VLDL) were reduced by LED compared to control group (P=0.000 and P=0.001, respectively). At end of study mean TG was within the reference value for patients with heart disease (2.0 mmol/L).

Of the measured inflammatory markers only CRP changed due to treatment (-16.50% ± 57.83 versus 33.07% ± 136.81 (P=0.010)). There was no effect of treatment on plasma insulin or glucose, but insulin requirement fell by at least 60% from baseline to end of study in patients treated with insulin. There was no difference between groups in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) baseline concentrations (DK centre only) or in effect of treatment in either NT-proBNP or BNP (data not shown).

There were no changes in renal parameters, or cardiac ejection fraction (only measured in UK center).

Discussion

The weight loss induced by LED in obese patients with moderate-to-severe HF and IHD in the present study is similar to other reports [21,22]. The degree of weight loss of ≈14 kg, of which 9.4 kg was FM associated with improved in physical and cardiac performance are likely to predict improved survival [13].

Earlier studies investigating the effects of therapeutic weight loss in obese HF patients all found positive effects of intentional weight loss on physical performance and cardiovascular risk markers [3,17]. Alpert et al. monitored the effect of gastric surgery in morbidly obese younger patients (≈38 years) with or without HF [3]. They observed the same improvements in cardiovascular risk markers in both groups, and no adverse effects of the rapid and large weight loss in either group. A single case study found HF and left ventricular ejection fraction to be improved after extreme weight loss achieved with LED diet over three years [23]. A small scale controlled intervention study in HF patients found 10 kg weight loss after a 12 week high protein diet, and improvements in cardiovascular risk factors and physical performance, measured as 6-MWT and VO2max [17].

In the present study change in BMI was predictive of the improvements in 6-MWT, as found previously [24]. Two other studies have investigated the effect of weight loss on physical performance [25,26]. One was a retrospective study that monitored the effect on obese HF out-patients of a rehabilitation program including weight loss [25]. They found that the 45 patients who complied with the program lost 5 kg in weight and improved exercise capacity. Those who did not lose weight (N=81) showed no change in exercise capacity. The other study found that an intervention of at least four weekly low-level exercise sessions (60% aerobic) in moderate-to-severe overweight HF patients only improved cardiopulmonary fitness in those who lost 5% weight or more (26). In another study of exercise, overweight HF patients increased their VO2max regardless of weight loss. Overall, the suggests that the positive effects of exercise on physical performance are increased by weight loss [25].

In the present study we found that treatment of patients with HF and IHD with LED reduced the level of CRP. Higher levels of CRP are associated with more severe heart failure, and are independently associated with mortality and morbidity. Weight loss has previously been shown to reduce CRP, but to a lesser extent than found in the present study [27], though the reduction in CRP is similar to that seen in subjects compliant with a low glycaemic diet after LED [28].

During the present study the Danish control group lost 1.2 kg ± 1.8 (P=0.002), and at the same time their physical performance deteriorated by 22.1% ± 25.6. Evangelista et al. found a similar reduction in 6-MWT in a control group that lost 1.5 kg over 12 weeks [17]. It is likely that this deterioration in 6-MWT reflects the natural history of HF supported by the fact that the weight loss in the control group was unintentional and primarily consisted of FFM.

There are no reports of adverse events associated with intentional weight loss in overweight HF, not even in association with weight loss of 33-50% of initial body weight [3,17,23,25]. On the contrary, intentional weight loss and improvement of

physical performance has been shown to reduce rate of re-ad-
mittance to hospital, improve quality of life, and reduce risk of all-cause mortality [26,29]. Experience from bariatric surgery, cardiovascular risks and impaired cardiac performance are common in patients, has shown that weight loss reduces cardiovascular events [30]. Despite these findings some consider that weight loss in obese HF patients "may even be potentially harmful" [4], and that "severe calorie restriction in patients with severe HF has the potential to worsen cardiac muscle function" [31]. The study referred to is by Alden et al, who found significant cardiac atrophy after intentional weight loss [32]. However, this was an animal study conducted in 11 dogs with results analysed after three weeks of acute protein-calorie restriction resulting in a 20-25% weight loss. These findings cannot be compared with the effect of an intentional weight loss achieved with a nutritionally complete (except for energy) diet of 750-1200 kcal per day provided by a well-formulated LED or energy restricted reintroduction.

In the present study treatment significantly reduced TG and VLDL. At the end of the study only two subjects had TG levels above the reference value for patients with cardiovascular disease, the median value being within the reference. The small changes seen probably reflect that 14 of the subjects in the intervention group were treated with statins.

The weaknesses of this study include the small sample size that itself was composed by combining two separate studies and this could have caused type I error. Recruitment at both DK and UK centres proved difficult: only few patients at the sites met inclusion criterion and of those many declined in part due to difficulty of transport to and from the centres; since both studies had similar objectives and interventions we felt it appropriate to merge the data. The UK centre was uncontrolled (it was designed as a pilot for a fully powered trial). The use of two different assessment methods of body composition might have weakened our results, as the correlation between the four-component model and bioelectric impedance is moderate [33], though both methods have been found to be capable of detecting change in body composition during weight loss [33]. The two centres analysed blood samples separately, and hence there may be inconsistency in the crude data. We have attempted to correct for bias, at least to some extent, by calculating the crude changes and the percentages, and including both in the statistical. Despite these limitations, robust and clinically important outcomes were observed.

The changes found in physical performance and cardiovascular risk markers indicate a beneficial effect of using LED in the treatment of moderate-to-severe HF and IHD patients. While this study was of short duration, it does demonstrate the safety of prescribing a high protein LED that is nutritionally complete apart from reduced energy for these patients, and the considerable benefits obtained by a substantial weight loss. Long-term outcome studies are needed to investigate if these short-term benefits translate into reduced cardiovascular events and mortality.

Statement of Authorship

The trial performed at the DK centre was designed by NRWG, SMHL, CTP, SS and AA, performed by NRWG and SMHL, and MRA was in charge of all biochemical analyses. The trial performed at the UK centre was designed by KSM and NF, performed by KSM, and PH performed echocardiogram. KSM, NF and KD interpreted the results in the UK centre. NRWG performed all the statistical work and prepared the data for the present manuscript. All authors participated in the interpretation of the results and critically reviewed and approved the manuscript.

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Conflict of interest

None declared.

Supplementary information is available at the journal’s web-site.

Non-standard abbreviations

6-MWT: six minute walk test; BMI: body mass index; BNP: brain natriuretic peptide; CRP: C-reactive protein; HC: hip circumference; HDL: high density lipoprotein; IHD: ischaemic heart disease; FFM: fat free mass; FM: fat mass; LDL: low density lipoprotein; IQR: inter quartile range; LED: low energy diet; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; TG: triglycerides; VLDV: very low density lipoprotein, VO2max: maximum oxygen uptake; WC: waist circumference.

References


