Clinical research

Effect of obesity and being overweight on long-term mortality in congestive heart failure: influence of left ventricular systolic function

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Aims Previous studies have suggested that a high body mass index (BMI) is associated with an improved outcome in congestive heart failure (CHF). However, the studies addressing this problem have not included enough patients with non-systolic heart failure to evaluate how left ventricular systolic function interacts with obesity on prognosis in CHF. The aim of this study was to evaluate how BMI influences mortality in patients hospitalized with CHF, and to address in particular whether the effect of BMI is influenced by left ventricular (LV) systolic function.

Methods and results Retrospective analysis of baseline and survival data for 4700 hospitalized CHF patients for whom BMI was available. LV systolic function, as assessed by wall motion index was available for 95% of the patients. Follow-up time ranged from 5 to 8 years. In the total population, the risk of death decreased steadily with increasing BMI from the underweight to the obese. Compared with normal weight, and adjusted for sex and age, risk ratios (RR) and 95% confidence limits were: underweight 1.56 (1.33–1.84), overweight 0.90 (0.83–0.97), obese 0.77 (0.70–0.86). Being underweight conferred a greater risk in CHF patients with normal systolic function [RR 1.66 (1.29–2.14), compared with normal weight] than in patients with reduced systolic function [RR 1.11 (0.87–1.42), P for interaction 0.03]. In patients with systolic dysfunction, obesity was associated with increased risk compared with normal weight [RR 1.21 (1.01–1.45)].

Conclusion Increasing BMI in CHF is associated with a lower mortality, but the influence is complex and depends on left ventricular systolic function. Hence, in patients with systolic dysfunction obesity may indicate an increased risk.
Introduction

Obesity and being overweight and are well known risk factors for development of congestive heart failure (CHF). Given the fact that the incidence and prevalence of both obesity and CHF are increasing rapidly in the western world, the two conditions are likely to co-exist in a patient. Indeed, it has been shown in several cohorts of CHF patients that 29–62% are overweight, 15–37% are obese. In the general population, obesity is associated with an increased mortality, but paradoxically a positive correlation between body mass index (BMI) and survival in CHF patients has been reported. However, some investigators have not found any significant difference in survival between normal weight and obese CHF patients, and others have reported a U-shaped relation between BMI and mortality. The studies which have addressed the influence of BMI on survival in CHF generally only included patients with left ventricular (LV) systolic dysfunction, or did not provide information about LV systolic function. In cohorts of unselected CHF patients, ~50% are reported to have normal systolic function. Clinical characteristics of patients with non-systolic heart failure are significantly different from patients with reduced left ventricular ejection fraction, particularly with regard to gender and age. Consequently, results obtained in epidemiological studies restricted to patients with LV systolic dysfunction cannot readily be extrapolated to the general CHF population. Furthermore, the clinical diagnosis of CHF may be particularly difficult to establish in obese individuals. For these reasons it seems of interest to evaluate the effect of BMI on survival in a more unselected cohort of CHF patients in whom information about LV systolic function is available. Using a large database on consecutive patients admitted to hospital with new or worsening CHF, the aim of the present study was to evaluate the effect of BMI on survival and in particular to explore the influence of normal versus abnormal LV systolic function on this effect.

Methods

Patients were recruited from the population screened for the DIAMOND (Danish Investigations of Arrhythmia and Mortality)-CHF study. The design of the DIAMOND study has been described previously. This study was a multi-centre, randomized, double blind, placebo controlled trial of the efficacy of the class III anti-arrhythmic agent dofetilide on mortality in patients with CHF. Twenty-seven percent of the screened population was eventually randomized in the drug trial. The trial showed no significant effect of dofetilide when compared with placebo. Screening for the study was conducted at departments of cardiology or internal medicine in 34 hospitals in Denmark. A total of 5548 consecutive patients hospitalized with new or worsening CHF were screened for entry into the study between November 1993 and July 1996. These patients comprise the DIAMOND-CHF screening registry. Inclusion into the DIAMOND-CHF registry required that a clinical diagnosis of heart failure had been made by the local investigators and that the patient had experienced at least one episode of shortness of breath within the preceding month, either on minimal exertion or at rest [corresponding to New York Heart Association (NYHA) functional class III or IV], or paroxysmal nocturnal dyspnoea. Patients with CHF who are less symptomatic are not likely to be admitted to hospital for heart failure in Denmark, and as such the screened population probably represents the vast majority of patients hospitalized with new or worsening heart failure. Patients with acute myocardial infarction within the last 7 days were excluded from the DIAMOND-CHF screening registry. At the time of screening the investigators obtained a clinical history, a physical examination and an ECG. Body weight and height were also recorded. Furthermore, an echocardiogram was recorded on videotape and sent to a core laboratory for evaluation. LV systolic function was assessed by calculation of wall motion index (WMI) as described previously using a 16-segment model of the left ventricle and a reverse scoring system. An estimate of LV ejection fraction can be obtained by multiplying wall motion index by 0.3. In the present study, significant LV systolic dysfunction was defined as WMI ≤ 1.2 (LV ejection fraction approximately < 0.35). Measurements of left ventricular end-diastolic diameter were obtained from 2D recordings (apical 2-chamber view). Creatinine clearance was calculated from serum creatinine values using the formula by Cockcroft and Gault. Information about hypertension, ischaemic heart disease, previous myocardial infarction, diabetes and valve disease was based on patient interview and chart review. No pulmonary function tests were universally available and therefore the presence or absence of chronic obstructive pulmonary disease was decided by the local investigator based on chart review.

Statistical analysis

Patients were categorized into four groups of body mass indices using the nomenclature proposed by the WHO: BMI < 18.5 kg/m² = underweight; 18.5 kg/m² ≤ BMI < 25 kg/m² = normal weight; 25 kg/m² ≤ BMI < 30 kg/m² = overweight; ≥ 30 kg/m² = obesity. Continuous baseline variables are presented as medians with 5–95% percentiles and were compared among the different weight groups using Kruskal–Wallis tests. Discrete variables were compared by the continuity adjusted χ² test. All tests were two-sided. The Kaplan–Meier method was used to construct life-table plots. Relative risks (RR) and 95% confidence intervals (CI) were calculated as hazard ratios obtained from Cox proportional-hazard models. BMI was entered as a grouped variable rather than as a continuous variable since it did not entirely fulfill the criteria for proportional hazard when entered as such. Multivariable models were constructed using the available clinical covariates. Medical treatment was not added to the model as this could potentially introduce selection bias given the fact that the patients were not randomized to their treatment regimen. Also, LV end-diastolic diameter was excluded from the model because this variable is closely correlated to BMI. The models fulfilled the criteria for proportional hazard. Subsequently, significant predictors of mortality in the multi-variable model were identified using a backward selection
procedure. All variables from Table 1 (excluding medical therapy and left ventricular end-diastolic diameter (LVEDD)) were included in the original multi-variable model using two WMI-dummy variables (for WMI > 1.2 and WMI ≤ 1.2) and applying a backward selection procedure. Values with a P-value > 0.01 were then removed, and the model was repeated without backward selection in the two WMI strata. Linearity was checked by including continuous variables both as such and grouped according to quintiles. Absence of effect of the grouped variable indicated that the effect was linear. Overall model fit was evaluated using likelihood ratio tests. Interaction analysis was performed using a likelihood ratio test in a multi-variable Cox model. Testing for interaction was performed for all variables included in Table 1, except medication and LVEDD. All calculations were made using the Statistical Analysis System software (SAS Institute, Cary, NC, USA). A P-value < 0.05 was considered significant.

Results

Baseline characteristics of the 4700 patients according to BMI groups using WHO definitions are presented in Table 1. Males were overrepresented among the overweight and obese. There was a clear inverse relationship between age and BMI. Chronic obstructive pulmonary disease and smoking was much more common among the underweight and, as expected, the prevalence of diabetes and hypertension increased steadily with increasing BMI. Significant LV systolic dysfunction was less common among the overweight and obese patients. As expected, LVEDD was greater in the larger patients. Echocardiographic evaluation was less frequently available in obese individuals (93 vs. 96% in normal weight patients). There was no significant difference among the BMI groups with regard to NYHA function class, and this was mirrored in a fairly equal use of loop diuretics in all groups. Rates of ACE-inhibitor use were similar in all groups, except for a slightly lower value in the overweight patients in whom a higher rate of significant renal dysfunction was also

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of 4700 patients admitted to hospital with heart failure according to BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight (BMI &lt; 18.5 kg/m², n = 196)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>60 (31)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76 (58–88)</td>
</tr>
<tr>
<td>Duration of CHF (months)</td>
<td>12 (0.1–144)</td>
</tr>
<tr>
<td>History of IHS (%)</td>
<td>112 (57)</td>
</tr>
<tr>
<td>Valve disease (%)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Cr-Cl ≤ 20 mL/min (%)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (%)</td>
<td>69 (35)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>90 (47)</td>
</tr>
<tr>
<td>NYHA III–IV (%)</td>
<td>133 (69)</td>
</tr>
<tr>
<td>WMI 1.2 (%)</td>
<td>98 (51)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>48 (32–62)</td>
</tr>
<tr>
<td>Treatment at discharge ACE-I (%)</td>
<td>88 (45)</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>120 (61)</td>
</tr>
<tr>
<td>Betablocker (%)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Loop diuretic (%)</td>
<td>170 (87)</td>
</tr>
</tbody>
</table>

Median and 5–95% percentiles. IHS: ischaemic heart disease; Cr-Cl: creatinine clearance.

Figure 1: Mortality rate in 4700 patients with CHF according to their body mass index at baseline; P < 0.0001 for underweight, overweight and obese in comparison with normal weight (Log rank test).
encountered. The data demonstrate a clear inverse relationship between digoxin use and BMI. More overweight and obese patients received beta-blockers but the overall use of this class of agents was low.

When the baseline characteristics of the 4700 patients included in the present study were compared with those of the 791 patients for whom BMI was unavailable, some significant differences were found. Among the patients without a recorded BMI, female gender was more common (48 vs. 39%), whereas ischaemic heart disease was less prevalent (49 vs. 58%). Furthermore, fewer had creatinine clearance > 60 mL/min (31 vs. 38%), and there were more patients with WMI > 1.2 (67 vs. 58%) (P < 0.001 for all) among the patients without recorded BMI.

As shown in Figure 1 mortality rates were inversely related to increased BMI (P < 0.001). In a Cox model containing only the BMI groups, risk ratios (95% CI) for death compared with normal weight were: underweight 1.48 (1.26–1.74), overweight 0.83 (0.77–0.90), obese 0.62 (0.56–0.69). When these risks were adjusted for differences in age and gender results were fairly similar: underweight 1.56 (1.33–1.84), overweight 0.90 (0.83–0.97), obese 0.77 (0.70–0.86). In a multi-variable model containing the covariates listed in Table 1, except medical therapy and left ventricular end-diastolic diameter, significant interaction was found between BMI and WMI (P = 0.03) and between BMI and chronic obstructive pulmonary disease (P = 0.01). For this reason, risk ratios for death in the different BMI groups, which have been controlled for the impact of covariates described above, are presented with respect to the presence or absence of chronic obstructive pulmonary disease and the presence or absence of LV systolic dysfunction (Table 2). Figure 2 shows the Kaplan–Meier plot for patients with LV systolic dysfunction and for those with normal or near normal systolic function. In the multi-variable Cox models the interactions are complex both with regard to WMI and chronic obstructive pulmonary disease. In patients with LV systolic dysfunction the presence of overweight or obesity actually conferred an excess risk, whereas in those with non-systolic heart failure, the heavier patients had a lower mortality rate (based on evaluation of RR in the multivariable Cox model, Table 2). Multi-variable analyses performed using WMI = 1.6 as cut-off value for systolic dysfunction instead of 1.2 yielded similar results with regards to RR and CI (data not shown). Being underweight was associated with a greater risk for patients with chronic obstructive pulmonary disease than in those without obstructive airway disease. In contrast, for patients with an above normal BMI, the risk estimates associated with high BMI were lower in patients with chronic obstructive pulmonary disease than in those without. Nevertheless, when data were stratified according to the presence of chronic obstructive pulmonary disease, all risk estimates in patients with BMI > 25 were close to 1.

## Discussion

The main finding of the study is that mortality is inversely related to BMI in patients hospitalized with CHF, but furthermore that the effect of BMI on prognosis in CHF depends on the systolic function of the left ventricle as well as the presence or absence of co-existing chronic obstructive pulmonary disease.

### Baseline characteristics

In the present study several baseline variables were unevenly distributed in different weight groups. Overweight and obese patients were younger than under and normal weight patients, consistent with the study by Lavie et al. Other studies have not confirmed this finding. In keeping with the fact that underweight patients were older, female patients were overrepresented among the patients with low BMI. This is in line with one previous study, but not with other studies dedicated to the analysis of BMI and prognosis in CHF. This discrepancy is likely to be due to the fact that the latter studies included very few female patients.

Hypertension and diabetes are well known to be associated with obesity and these relationships were also evident in the current study. We found a close

### Table 2: Effect of BMI on the relative risk of death during follow-up in subgroups for variables interacting significantly with BMI

<table>
<thead>
<tr>
<th>Underweight (BMI &lt; 18.5 kg/m²)</th>
<th>Normal weight (18.5 ≤ BMI &lt; 25 kg/m²)</th>
<th>Overweight (25 ≤ BMI &lt; 30 kg/m²)</th>
<th>Obese (BMI ≥ 30 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Reference value</td>
<td>n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>---</td>
<td>-----------------</td>
<td>---</td>
<td>-------------</td>
</tr>
<tr>
<td>WMI ≤ 1.2</td>
<td>98</td>
<td>1.11 (0.87–1.42)</td>
<td>855</td>
</tr>
<tr>
<td>WMI &gt; 1.2</td>
<td>93</td>
<td>1.66 (1.29–2.14)</td>
<td>1034</td>
</tr>
<tr>
<td>History of chronic obstructive pulmonary disease</td>
<td>69</td>
<td>1.76 (1.30–2.40)</td>
<td>441</td>
</tr>
<tr>
<td>No history of chronic obstructive pulmonary disease</td>
<td>127</td>
<td>1.09 (0.88–1.35)</td>
<td>1517</td>
</tr>
</tbody>
</table>

The multi-variable Cox models include all covariates mentioned in Table 1, except LV end-diastolic diameter and medical treatment. Overall model fit: P < 0.0001 for all models (likelihood ratio test).
prevalence of smoking was lower among underweight than among normal and overweight patients. The presence of chronic obstructive pulmonary disease was not reported in any of the previous studies.

The difference in treatment with digoxin among patients with low and high BMI probably reflects that atrial fibrillation was more common among the underweight (22 vs. 20% in the obese, \( P < 0.001 \)). The latter was, in turn, most likely attributable to the positive correlation between WMI and BMI, since it has been reported that the prevalence of atrial fibrillation is inversely related to LV systolic function in CHF. The finding of a low overall rate of beta-blocker use is explained by the fact that data were collected before firm evidence for the benefit of beta-blockade in CHF had been documented.

**Mortality**

In the present study of consecutive patients admitted to hospital with new or worsening CHF it was clearly demonstrated that long-term mortality was inversely related to BMI. A positive correlation between BMI and survival, as seen in our study, was observed more than 10 years ago in the Framingham study although the difference in mortality was not statistically significant. A similar and statistically significant positive effect of increasing BMI on survival was subsequently reported in another population-based registry, the Rotterdam Study. More recently, a number of studies with more selective inclusion criteria have demonstrated a lower mortality or number of major events in overweight or obese CHF patients. The patients included in these studies were all referred to secondary or tertiary centres, in most cases for heart transplant evaluation or specific exercise testing protocols. To our knowledge, the present study is the first to evaluate the effect of BMI in consecutive patients hospitalized with CHF. The study demonstrated an interaction between LV systolic function and BMI on the prognosis in CHF. For patients with normal or near normal LV systolic function, survival increased with increasing BMI, whereas for patients with LV systolic dysfunction survival rate followed a U-shaped curve with the lowest rate of death in normal weight patients. This interaction has not been tested in previous studies in which LV systolic dysfunction was an inclusion criteria or no information of LV systolic function was available. The study by Davos did include some patients with normal LV systolic function (<20%), but a possible interaction between left ventricular ejection fraction and BMI was not explored. The present study further demonstrates that the effect of BMI on mortality depends on whether or not the patient has chronic obstructive pulmonary disease. In particular, underweight CHF patients with chronic obstructive pulmonary disease are at very high risk. From population studies it is well known that low BMI is one of the major determinants of poor prognosis in chronic obstructive pulmonary disease patients, and apparently this excess risk is evident also in patients who have a primary CHF diagnosis.
In agreement with previous studies the present analysis shows that high BMI is associated with a better outcome in CHF patients in general. This finding represents a paradox to some extent,25 since obesity in general is considered to be associated with an increased cardiovascular risk. In line with this, our study suggests that the effect of BMI on survival is complex, implying that a major part of the effect of BMI on mortality is due to a high risk in cachectic patients, and also that the effect of overweight and obesity at least to some extent may be attributed to confounding by LV systolic function and chronic obstructive pulmonary disease. Moreover, contradicting a causal and beneficial effect of obesity on prognosis in CHF are results from smaller studies which have demonstrated a positive effect of intended weight reduction on symptoms and cardiac dimensions in CHF patients with morbid obesity.26 This effect in highly obese patients should not be confused with the well described detrimental effect of weight loss in normal weight patients with severe CHF (cardiac cachexia).27 There are, as of yet, no studies on the effect on mortality of intended weight reduction in obese patients with CHF. Therefore, the question about causality cannot currently be satisfactorily answered.

Although the overall findings of the present study are in agreement with most previous analyses, results for the subgroup of patients with systolic dysfunction are in contrast to the findings of some studies, which have exclusively studied this group of patients. Hence, in the DIAMOND registry normal BMI was associated with the lowest mortality in patients with LV systolic dysfunction, whereas others have shown either similar,8,20 or lower6 mortality or number of major adverse events in obese compared with lean individuals with low LVEF. The reason for this discrepancy is not clear. However, there are considerable differences in study populations. Unlike the patients in previous studies of the effect of BMI on survival, patients in the DIAMOND registry were older and were hospitalized. Therefore the subgroup of patients with LV systolic dysfunction in the present study may represent a more advanced degree of heart failure and possibly also of co-morbid conditions. It could be speculated that the potential role body composition may play in determining long-term prognosis is different in younger ambulatory patients. There are, however, currently no data to support such a theory.

Limitations

In the present study, a centralized off-line evaluation of LV systolic function, as estimated by wall motion index, was available in 95% of the patients. As expected, the proportion of echocardiograms that could be evaluated was lower among overweight and obese patients, reflecting the technical difficulties associated with cardiac ultrasound imaging in large subjects. However, the size of the problem was modest since even in the obese patients a WMI was recorded in 93%. Of greater potential concern is the validity of the clinical CHF diagnosis in obese patients with normal LV systolic function. Hence, in some obese individuals it may be difficult to determine whether the patient’s dyspnoea is cardiac in origin or merely a consequence of dyspnoea in obese individuals. Similarly, peripheral oedema may be caused by venous insufficiency related to obesity rather than reflect fluid retention due to poor cardiac function. In fact, some studies have suggested that the symptoms of dyspnoea in obese patients with heart failure, who have normal LV systolic function, is caused by obesity per se.8,29 In our study, it was clear that preserved LV systolic function was more common among overweight patients. It is possible that some of these patients were misdiagnosed as having heart failure. However, it should be noted that the incidence of hypertension and diabetes was higher in the obese patients. Both are important risk factors for development of diastolic dysfunction,30 and as such they may explain the over representation of non-systolic heart failure among the patients with high BMI. In the present study, no echocardiographic measures of diastolic function were obtained and therefore it is not possible to determine if isolated LV diastolic dysfunction can account for the higher proportion of apparent non-systolic heart failure in the obese patients with normal ejection fraction.

Several prognostic factors, such as serum cholesterol, peak oxygen consumption, serum sodium and natriuretic peptides were not measured in the DIAMOND registry and this, of course, is a limitation of the results obtained in the multi-variable analyses. Consequently, the degree of independence of BMI as a prognostic variable in CHF demonstrated in the present study must be viewed in the context of the clinical variables entered into the Cox model. Whether or not BMI would retain its prognostic information in models containing this supplemental information must be evaluated in future studies.

It should also be recognized that some of the variables, which were entered into the linear multi-variable models, such as diabetes, hypertension and obesity, are probably not independent. However, the fact that these variables are individually important risk factors mandated their presence in the models. The interactions analyses relating to the effect of chronic obstructive pulmonary disease may be limited by the fact that chronic obstructive pulmonary disease may be limited by the fact that chronic obstructive pulmonary disease could only be entered as a dichotomous variable since no pulmonary function test results were available. It could be speculated that chronic obstructive pulmonary disease with only minor reduction in FEV1 would have little impact on the effect of BMI on mortality, whereas severely reduced measures of ventilatory function would affect the relation to a greater extent. Further studies including pulmonary function testing are required to resolve this issue.

Finally, it should be acknowledged that multiple risk ratios were generated by the Cox analyses in the subgroups of WMI and chronic obstructive pulmonary disease. This introduces greater risk of finding a significant effect by chance, and therefore the results of the Cox analyses in the subgroups should be regarded as hypothesis generating. In this context it should be emphasized, however, that the dataset is large, and this is likely to reduce the risk of detecting a significant risk ratio by chance.
Conclusions

In hospitalized patients with CHF, mortality is inversely related to BMI, even when adjusted for differences in age and sex. However, it appears that the effect of BMI on prognosis in CHF depends on the systolic function of the left ventricle as well as the presence or absence of co-existing chronic obstructive pulmonary disease. Clearly, more studies of the association between BMI and survival in these subgroups with CHF are required. However, it seems well documented that a paradoxical positive correlation between BMI and survival is present at least in some groups of CHF patients. Whether or not the effect of obesity on survival in these groups is causal will require longitudinal and preferably intervention studies of weight reduction in obese CHF individuals.

References