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**Is there any survival advantage of obesity in Southern European haemodialysis patients?**

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**Abstract**

**Background.** In the general population, a high body mass index (BMI) is associated with increased cardiovascular disease and all-cause mortality. However, according to US epidemiological evaluation in maintenance haemodialysis (HD) patients, a reverse epidemiology is described and baseline obesity appears paradoxically associated with better survival. The aim of this study is to examine in a Southern European HD population the relationship between survival and BMI at the start of HD treatment, and how survival is influenced by the body weight (BW) variations during the first year of treatment.

**Methods.** A total of 85 dialysis centres located in Portugal, France and Italy and belonging to the FME European dialysis chain were included. The current prospective analysis focuses on incident patients admitted to these centres between 1 January 2000 and 30 September 2005 with <1 month of previous follow-up on RRT. Data were gained from the FME EuCliD database. Patients were classified at baseline in four categories according to the BMI: underweight, normal range, overweight and obese. Also, the patient survival was analysed according to five quintiles of BW changes during the first year of HD treatment: \(<-5.8\%\), \([-5.8 \text{ to } -1.1\%\), \([-1.1 \text{ to } 1.7\%\) (reference category), \([+1.7 \text{ to } +5.5\%\) and \(> +5.5\%\). Survival analysis was adjusted for a set of demographic and comorbidities using Kaplan–Meier curves and Cox model. Hazard ratios and their 95% confidence intervals were calculated with the use of the estimated regression coefficients and their standard errors.

**Results.** A total of 5592 patients were analysed (40.9\% females), and the mean age at admission was 64.4 ± 16.5 years. Of them, 27.7\% were diabetic. The mean follow-up was 2.0 ± 1.6 years. Almost half of the patients (46.4\%) were in the normal range of BMI (20–24.9 kg/m²). When analysed with the Cox model, the categories of baseline BMI (underweight, normal range, overweight and obese) significantly influenced the survival with the respective hazard ratio (HR) and confidence interval at 1.14 (0.96–1.35), 1.074 (0.67–0.9) and 0.78 (0.56–0.87). The strength of the association as well as the shape of the curve remains
Importance of Nutrition in This Setting.

Increased body weight (BW) variation during the first year of haemodialysis (HD) treatment is associated with patient survival, highlighting the importance of nutrition in this setting.

Conclusions. Despite increased comorbidities, overweight and obese patients on maintenance HD carry a significant lower mortality risk than patients in the normal and lower BMI ranges. This confirms the reverse epidemiology previously reported in US HD patients for these categories of BMI. Also, BW variation during the first year of HD treatment is associated with patient survival, highlighting the importance of nutrition in this setting.

Keywords: body mass index; body weight change; haemodialysis; nutrition; survival

Introduction

In the general population, being overweight and obese is found to be associated with the increased prevalence of cardiovascular disease and overall causes of mortality [1]. However, in haemodialysis (HD) patients, an unusual relationship between body mass index (BMI) and survival was reported for the first time almost 25 years ago [2] with increased mortality in patients with low BMI and no increased mortality in overweight and obese HD patients. More recently, this association was reported in US HD patients, showing an inverse linear relationship between survival and BMI, that is a survival advantage, even in morbidly obese patients [3]. Also, since the Diaphane study, the DOPPS study has reported this type of relationship in a set of US and European patients [4]. This inverse and unexpected correlation is part of the recent concept called reverse epidemiology, reported also for instance with predialysis blood pressure [5] and that has been thoroughly reviewed [6]. Nevertheless, the inverse relationship between BMI and survival in HD patients is not universally recognized. Several studies have failed to find this association in Asian patients like in Japan [7] or among Asian American HD patients [8,9]. The first objective of our study was to examine the relationship between BMI and survival in Southern European incident HD patients whereby the case-mix of the dialysis population has changed dramatically since the DIAPHANE study and because the epidemiology of cardiovascular disease and especially coronary artery disease (CAD) is dramatically different between the US and Northern and Southern Europe [10]. The second objective was to evaluate the effect of the body weight (BW) variation during the first year of HD treatment on the prognosis of maintenance HD patients.

Patients and methods

This prospective study included 76 dialysis centres owned by Fresenius Medical Care (Bad Homburg, Germany) in Italy, Portugal, and France (see the Appendix). All incident end-stage renal disease (ESRD) patients, with less than 1-month previous HD treatment in another facility, were included in the study between 1 January 2000 and 30 September 2005. Amputated patients were excluded from analysis in order to avoid miscalculation of BMI. Data were retrieved from the EuCliD (European Clinical Database) database that is updated monthly with patient characteristics including demographics, comorbidities, dialysis prescriptions, ancillary therapies, lab results and outcome. At the start of HD, the patients were categorized into five categories of BMI: BMI <20, 20–24.99, 25–29.99 and >30 kg/m². The upper two categories corresponded to the WHO standard classification of overweight (25–29.99 kg/m²) and obese (≥30 kg/m²).

According to the general acceptance and also in order to have meaningful numbers, a BMI <20 was defined as being underweight, and BMI = 20–24.99 was considered to be normal weight. The comorbid conditions present in the study were defined according to the International Classification of Diseases, tenth revision code (ICD-10): CAD (I20-I25, Z95.1, Z95.5), heart failure (I50-I51, I13-I13.2, I42-I42.2, I42.6-I42.7, 111.0, 111.9, 197.1, 197.8, I42.9, I43.2), valvular heart disease (Z95.2, Z95.3, Z95.4, Z95.9, 101.1, 105.0, 108.9, 109.1, 109.8, I33.0, I38, I39.8, I39.9, I82.0, Z48.8, Z95.9, T82.6, 145.2, 145.3, 145.6-147.9, I49-3-I49.9, I49.3-I49.9, I49.1-144.3, I48, I49.0, I34-I37.9, I39-I39.4), atherosclerosis disease (I70-I76.9), cerebrovascular disease (I60-I69), pulmonary disease (J41-J47.9, J96), depression (F32.1-F33.9, F06.3, F20.4, F25.1, F31.3, F31.9), cancer/neoplastic disease (C0-C07.9, D37-D48.9) and severe liver disease (K70-K77.9).

Distribution of comorbidities was analysed in each BMI category and according to age (below and above the age of 65). Survival was studied among the different BMI ranges and adjusted for the different comorbidities. Also, survival from the second year of treatment has been analysed according to the evolution of the BW during the first year of HD treatment. Patients were split into five quintiles according to this evolution expressed as a percentage normalized to the ideal BW (calculated from the Broca formula: ideal BW = (height in cm − 100) for males and ideal BW = (height in cm − 104) for females [11,12]): <-5.8%, -5.8 to -1.1%, -1.1 to 1.7% (reference category), +1.7 to +5.5% and >+5.5%.

Statistics

The mean values and frequencies of the parameters were compared by ANOVA or the chi-square test, as appropriate. Survival functions according to baseline BMI were described using the Kaplan–Meier technique. The log-rank test was used for univariable comparisons. Cox proportional hazard models were used to compare survival according to baseline BMI adjusting for a set of demographic and comorbidities.

All analyses were performed with adjustment for age, gender and for each of the following comorbidity indicators: diabetes, CAD, heart failure, valvular heart disease, atherosclerosis disease, cerebrovascular disease, pulmonary disease, depression, cancer/neoplastic disease and severe liver disease (Table 1). Only age has been introduced as a continuous variable, and all others as categorical variables (for gender: ref. females; for comorbidity indicators: ref. present-absent). Both Kaplan–Meier curves and Cox model used the same end-point (death), and patients were censored when they were changed to peritoneal dialysis therapy, were transferred to another dialysis unit, received a kidney graft or were still on extra-corporeal treatment on the final observation date (30 September 2005). All patient characteristics considered in the study were reported. When Cox proportional hazard regression was applied, all reported variables were used to obtain the final multivariate model. Estimated relative risks (hazard ratios) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with $P < 0.05$ considered significant. The proportion
BMI and survival of haemodialysis patients

Table 1. Patients’ characteristics according to the BMI distribution

<table>
<thead>
<tr>
<th></th>
<th>Underweight</th>
<th>Normal range</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number (%)</td>
<td>679 (13.9)</td>
<td>2261 (46.4)</td>
<td>1367 (28.0)</td>
<td>569 (11.7)</td>
</tr>
<tr>
<td>Age (years: mean ± SD)</td>
<td>65.7 ± 22.1</td>
<td>63.7 ± 16.7</td>
<td>65.2 ± 13.9</td>
<td>62.7 ± 13.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>46.7</td>
<td>24.2</td>
<td>30.8</td>
<td>43.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.0</td>
<td>11.1</td>
<td>13.8</td>
<td>13.7</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>13.7</td>
<td>13.4</td>
<td>14.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>6.8</td>
<td>6.6</td>
<td>7.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>8.0</td>
<td>5.4</td>
<td>6.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Atherosclerosis disease (%)</td>
<td>5.0</td>
<td>4.0</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>2.1</td>
<td>0.8</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Pulmonary disease (%)</td>
<td>8.7</td>
<td>6.7</td>
<td>5.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>1.2</td>
<td>0.8</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Cancer/neoplastic disease (%)</td>
<td>1.6</td>
<td>2.1</td>
<td>2.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

hazard assumption was checked for each model by inspection of the complementary log minus log plots. To evaluate the impact of the BW changes on mortality, patients surviving more than 1 year were selected. The behaviour of BW during the first year was evaluated, classifying the patients according to decrease or stability and the increase of dry BW. Then, survival analyses were modelled considering the behaviour of BW change during the first year of follow-up as a predictor of subsequent mortality. All statistical analyses were performed using the SPSS software, version 14 (SPSS Inc., Chicago, IL, USA).

Results

A total of 5592 patients were included in the study during this 57-month period. The average age was 64.4 ± 16.5 years and the mean follow-up 2.0 ± 1.6 years. Female gender represented 40.9% of the whole population. However, in obese patients, the proportion of female gender increased significantly (Table 1). The prevalence of diabetes was 27.7%, but the distribution of diabetic patients increased significantly in the overweight and obese BMI category (Table 1). The distribution of BMI among the studied patients is also shown in Table 1. Almost half of the patients (46.4%) were in the normal range of BMI (20–24.99 kg/m²). A BMI <20 (underweight category) was present in 13.9% of the patients. Overweight (BMI = 25–29.99 kg/m²) and obese (≥30) represented 28 and 11.7%, respectively. The prevalence of CAD was equally distributed in the different BMI ranges in maintenance HD patients over the age of 65. In younger patients below 65, CAD increased in overweight and obese patients compared to normal and underweight patients (Figure 1). The heart failure prevalence was significantly higher in the obese patients when compared to normal BMI patients, both below and over 65 years of age. The other BMI categories were not significantly different for the prevalence of this comorbidity.

The proportion of patients who were transplanted was 6.6% ranging from 5.2% in underweight to 7.3% in the normal range. The proportion of those transferred to peritoneal dialysis was 9.4% ranging from 8.9% in overweight to 10.6% in underweight. The total number of deaths during the follow-up was 1147 (23.5%). The Kaplan–Meier survival curve for the four BMI ranges is displayed in Figure 2. Survival was significantly better for overweight and obese patients compared to that for normal and underweight patients. In Figure 3 and Table 2, the unadjusted and adjusted relative risks of death are displayed for the four BMI categories, with the normal BMI range used as a reference. Overweight and obese patients had an adjusted hazard ratio of 0.78 (0.67–0.9) and 0.71 (0.56–0.87), respectively.
In this study, we confirm among a large prospective Southern European cohort of incident HD patients that a high BMI range in the overweight and obese is associated with better survival than in normal and underweight BMI categories. This unexpected relationship between BMI and survival had been previously suggested in French patients in 1982 by Degoulet et al. [2] in the DIAPHANE study. It was confirmed later by Fleischmann et al. [13] using different BW ranges, showing a clear survival advantage in patients with a BMI >27 kg/m², mostly in African American patients. Our findings in an incident HD patient cohort are close to what has been reported in incident [8,14] and prevalent US patients [3]. These latter reports used different categories of BMI, from simple (three ranges: <23.1, 23.1–27.8, >27.8 kg/m² [14]) to very sophisticated distribution (from <18 or 19 to >37 to 45 kg/m² in 8 to 11 categories [8,15]). The other studies [2,4,14] did not analyse specifically the issue of the morbidly obese patients. Our analysis was not able to confirm the survival advantage in morbidly obese patients, as reported by Kalantar-Zadeh et al. [15] because the number of patients in this category (BMI >40 kg/m²) was too small (0.7% of the total patients) and they were pooled with the 30–39.99 kg/m² category. Moreover, we report in the incident patients the distribution of severe comorbidities such as diabetes, CAD and heart failure. Adjustments for these comorbid conditions, absent in the Kalantar-Zadeh study [15], did not change the paradoxical relationship between BMI and patient survival. It confirms the findings of the DOPPS study [4] in which obese and overweight patients with high-risk comorbidities were found to have better survival than low and normal BMI patients with the same risk profile.

Studying the mortality among a cohort of Spanish HD patients, Marcen et al. [16] did not find any difference of BMI between the patients who survived and who died. However, in this prevalent cohort, the relationship between BMI and survival was not studied independently and was not adjusted for other factors such as age, vintage and comorbidities. More surprisingly, the Dutch NECOSAD study did not find advantages of a high BMI on the survival of incident female and male HD patients [17], whereas it reports the expected increased mortality risk in the low range of BMI (<18.5 kg/m²). However, this study only included patients between 50 and 65 years of age and used a BMI reference range of 22.5–25 kg/m². Even when these criteria are applied to our studied population, it does not change our

Discussion

The second part of the study was the report of survival according to the evolution of the BW during the first year of HD treatment. The patients were divided into five categories according to the quintile distribution: <−5.8%, −5.8 to −1.1%, −1.1 to 1.7% (reference category), +1.7 to +5.5% and >+5.5%. Table 3 reports the patient characteristics and the patient outcome of the studied population including the adjusted hazard risks and the corresponding 95% CI. Mortality was significantly higher in the lowest quintile, in patients who had a weight loss over 5.8% during the first year of HD treatment, whereas it was not influenced in other quintiles, in patients with a weight loss lower than 5.8%, or who remained stable or gained weight.

Table 2. Survival and BMI categories; crude and adjusted hazard ratios for the four BMI categories

<table>
<thead>
<tr>
<th>BMI categories</th>
<th>Crude hazard ratios</th>
<th>Adjusted hazard ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Underweight</td>
<td>1.23</td>
<td>1.08–1.49</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.85</td>
<td>0.74–0.98</td>
</tr>
<tr>
<td>Obese</td>
<td>0.79</td>
<td>0.65–0.97</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence intervals; BMI, body mass index.

Table 3. Characteristics and results of the survival analysis of the patients included in the survival analysis according to the evolution of body weight during the first year of HD treatment

<table>
<thead>
<tr>
<th>BW variation categories</th>
<th>Pts n</th>
<th>Age (years: mean ± SD)</th>
<th>Diabetes%</th>
<th>Cumulative survival at 3 years (%)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>−5.8%</td>
<td>516</td>
<td>65.9 ± 15.0</td>
<td>27.0</td>
<td>60.7</td>
<td>1.60</td>
<td>1.20–2.14</td>
</tr>
<tr>
<td>−5.8 to −1.1%</td>
<td>517</td>
<td>62.3 ± 16.0</td>
<td>21.7</td>
<td>79.7</td>
<td>0.85</td>
<td>0.62–1.16</td>
</tr>
<tr>
<td>−1.1 to +1.7%</td>
<td>516</td>
<td>61.8 ± 15.7</td>
<td>16.6</td>
<td>71.9</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>+1.7 to +5.5%</td>
<td>516</td>
<td>63.4 ± 20.9</td>
<td>16.8</td>
<td>77.7</td>
<td>0.77</td>
<td>0.56–1.06</td>
</tr>
<tr>
<td>&gt;+5.5%</td>
<td>517</td>
<td>62.9 ± 15.1</td>
<td>17.9</td>
<td>78.5</td>
<td>0.90</td>
<td>0.66–1.23</td>
</tr>
</tbody>
</table>

Pts, patients; n, number; HR, hazard ratio; CI, confidence intervals; BW, body weight.
ful findings and does not explain the discrepancy between the Dutch and Southern European dialysis patients regarding survival and BMI ranges. The explanation may be related to the difference of cardiovascular disease epidemiology between the Netherlands and Southern Europe. As reported by Levy and Kannel [10], the death rate from CAD in both sex and in the age range 35–74 is much lower in France, Spain and Portugal (three of the four countries involved in the current study) when compared to the Netherlands. A higher prevalence of cardiovascular disease in Dutch obese HD patients may blunt the survival advantage observed in Southern European obese HD patients, especially because young patients, aged between 18 and 50 years, were not included in the Dutch study. The high prevalence of cardiovascular disease in the studied age ranges may have outweighed the benefit of a high BMI.

We have also confirmed that a BW loss >5.8% (first quintile) during the first year of HD treatment was associated with significantly increased mortality. The second quintile (−5.8 to −1.1%) had no significant reduction in survival, whereas Kalantar-Zadeh et al. [15] reported that each category below −1% of BW loss had a significant increase in patient death. In this last study, prevalent patients were analysed whereas our cohort included only incident ones. Previous reports have shown a different evolution of BW in both prevalent and incident cohorts. In the HEMO study [18], prevalent HD patients displayed a progressive decline of BW all along the 3-year follow-up, whereas in patients starting HD [19,20], BW initially decreased during the first 2–4 months corresponding to the fluid removal and then increased again because of appetite recovery. Whereas in prevalent patients BW loss is mainly interpreted as progressive malnutrition, in incident patients it is possible that fluid removal for extracellular volume accumulated in the pre-dialysis period may interfere with the interpretation of the BW variation during the first year of treatment. This may explain why only an important BW loss >5.8% in incident HD patients is found to have a detrimental effect regarding survival, similar to other nutritional markers such as serum albumin and prealbumin whose lowest quartiles were associated with a higher mortality rate in a study by Combe et al. [21].

Trying to explain this paradoxical association of obesity with better survival among HD patients, Johansen et al. [8] ruled out from their data the influence of lean body mass and inflammation suggesting that fat itself might be protective in the catabolic condition of HD treatment. For Kwan and Beddhu [22], the paradox is related to the balance between the deleterious effect of adipose tissue (inflammation, increased associated comorbid conditions, ...) and the nutritional advantage of adiposity represented by fat tissue in the catabolic situation of HD treatment. Another hypothesis is raised by Sarkar et al. [23]. They have shown that the visceral compartment, also referred to as the high metabolic rate compartment, is inversely related to the BMI and is correlated with the protein catabolic rate, a surrogate of uraemic toxin generation. The interpretation is that patients with low BMI have a relatively higher production of uraemic toxins than high BMI patients, leading to decreased survival by higher or increased dialysis needs. However, this appealing hypothesis cannot be the unique explanation since reverse epidemiology for BMI also exists in other fields, like heart failure for instance [24]. Moreover, it has been recently reported that the reverse epidemiology concept regarding pre-dialysis blood pressure is time dependent [25] with an increased mortality risk associated with the low blood pressure level in the first 2 years of dialysis treatment followed by an increased risk of mortality associated with high blood pressure from the third year of HD treatment. This time-dependent relationship between BMI and mortality may exist but remains to be confirmed. That was not the case in the NECOSAD study in which the 7-year follow-up did not display any change in the relationship of BMI and survival, both in HD patients and normal subjects [17].

In conclusion, we confirm the reverse epidemiology regarding BMI and survival in incident Southern European HD patients even after adjustments for comorbidities, except in the case of morbid obesity. Also, it is confirmed that loosing weight during the first year of HD treatment is associated with an increased mortality risk. This stresses the pivotal role of nutritional issues in dialysis patients, and strengthens the need for the regular assessment of nutritional markers and nutritional intervention studies.

Acknowledgment. These data have been presented at the XLIII EDTA-ERA meeting (Glasgow, Scotland, July 2006).

Conflict of interest statement. All authors are employees or consultants of the chain of clinics quoted in the paper.

Appendix

Participating Centres: France


Participating Centres: Italy

NephroCare Dialnova, NephroCare Nephros Cassino, NephroCare Centro Dialisi Riviera del Conero, NephroCare Nefrosal, NephroCare Mirabial, NephroCare Malpighi, NephroCare Sodial, NephroCare Emodial Vesuvio, NephroCare SM2, NephroCare Emodial, NephroCare Nephros Venafro, NephroCare Alfabial, NephroCare Diaclecenter, NephroCare Ciletto Dial Dianoval, NephroCare Kidney, NephroCare Nefrodisal, NephroCare Ciletto Dial Olidial, NephroCare Renal Center, NephroCare Nedial, NephroCare Nedial Napoli, NephroCare Cercos, NephroCare Beta Dial, NephroCare Rusdial, NephroCare Omnia Dial, NephroCare Dial Torre, NephroCare Fanus c/o Clinica Ruesch, NephroCare Enne E, NephroCare Fanus
Soma Vesuviana, NephroCare Dialten, NephroCare Ruscosa, NephroCare Dialy Center, NephroCare II Nefrológico, NephroCare Centro Diagnostico e Terapeutico delle Malattie Renali.

Participating Centres: Portugal

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