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Original Article

Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Background. Haemodialysis (HD) patients with lower body mass index (BMI) have a higher relative mortality risk (RR), irrespective of race. However, only Asian Americans treated with HD have been found to have an elevated RR with higher BMI. Asian Americans on HD are 'healthier' than other race groups (i.e. have better overall survival). We hypothesized that an increased mortality risk might be associated with high BMI in a variety of other 'healthier' subgroups of HD patients.

Methods. The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) provided baseline demographic, comorbidity and BMI data on 9714 HD patients in the US and Europe (France, Germany, Italy, Spain, and the UK) from 1996–2000. Using multivariate survival analyses, we evaluated BMI–mortality relationships in HD subpopulations defined by continent, race (black and white), gender, tertiles of severity of illness (based on a score derived from comorbid conditions and serum albumin concentration), age (<45, 45–64, $\geqslant 65$), smoking, and diabetic status.

Results. Relative mortality risk decreased with increasing BMI. This was statistically significant ($P<0.007$) except for the smallest subgroup of patients who were <45 years old and were also in the healthiest tertile of comorbidity. All else equal, BMI <20 was consistently associated with the highest relative mortality risk. Overall a lower relative mortality risk (RR) as compared with BMI 23–24.9, was found for overweight (BMI 25–29.9; RR 0.84, $P=0.008$), for mild obesity (BMI 30–34.9; RR 0.73, $P=0.0003$), and for moderate obesity (BMI 35–39.9; RR 0.76, $P=0.02$).

Conclusion. In a wide variety of HD patient subgroups, differing with respect to their baseline health status, increasing body size correlates with a decreased mortality risk. This contrasts with the association between BMI and mortality in the general population, and deserves further study.

Keywords: body mass index; haemodialysis; mortality

Introduction

Body mass index (BMI) is a standardized measure calculated from an individual's weight in kilograms divided by the square of their height in meters (kg/m^2). BMI correlates, better than body weight alone, with direct measures of body 'fatness' or 'density' [1]. In US haemodialysis (HD)-treated patients, a lower BMI is consistently found to be a strong predictor of an elevated mortality risk [2–5]. In contrast, a higher BMI, either overweight or obesity, has generally not been associated with any increase in mortality risk, except in Asian Americans [2–5]. Outside of the US, there is a paucity of published data relating body size to mortality risk in contemporary dialysis patients.

In the US general population, overweight (BMI 25–30) and obesity (BMI $\geqslant 30$) appear as risk factors for cardiovascular, cancer, and all-cause mortality [6]. However, the relative increase in mortality risk associated with overweight and obesity (*vs* normal BMI 23–24.9 kg/m^2) is larger in 'healthier' individuals without, as compared with 'sicker' individuals with, a history of chronic disease and/or smoking [6].

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Conversely, being lean (lower BMI) predicts much smaller increases in mortality risk in 'healthier' subjects with no history of chronic disease or smoking [6]. Thus, it is hypothesized that as the overall health of a population decreases, high BMI may become weaker, and low BMI stronger as a predictor of increased mortality risk, all else equal.

This hypothesis can be extrapolated to HD-treated patients (Figure 1). As a group they have a very high burden of chronic illness, perhaps accounting for the failure of most prior studies to identify a mortality risk associated with high BMI. One subgroup of HD-treated patients, namely Asian Americans, does have a significant increase in mortality risk for high BMI [5]. As a subgroup of US HD patients, Asian Americans are on average 'healthier', as evidenced by a lower prevalence of comorbidities and an approximately 35% lower mortality risk, than white Americans [5]. Therefore, overall health status may also influence BMI–mortality relationships between HD patients. The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) [7] allows comparison of BMI–mortality relationships in the US and Europe and among a variety of 'healthier', as compared with 'sicker' HD patient subgroups, such as younger patients, never-smokers and those with less chronic illnesses (comorbidities).

Subjects and methods

Data source

The DOPPS is a prospective, international, observational study of HD practices and outcomes in seven countries, including France, Germany, Italy, Japan, Spain, the UK, and the US. A detailed description of the study design, sampling techniques, and data collection methods has been published [7]. In each country two-stage sampling was employed to select representative samples of HD facilities and then random samples of patients within each facility. The initial round of selected patients is a true prevalent cross-section. Patients who die or leave the study are replaced by a random selection from new patients who have initiated treatment at the same facility. This sample is enriched with more incident patients. Data collection instruments (translated into appropriate language), are shared across countries, and are available on request. A study coordinator in each dialysis centre performs data collection/abstraction. Patients, medical directors, and nurse managers complete additional questionnaires. Detailed practice pattern data, demographics, cause of end-stage renal disease (ESRD), medical and psychosocial history, and laboratory data are collected at the time of study enrolment. Longitudinal data collection at regular intervals of approximately 4 months updates laboratory data, dialysis prescription and the occurrence of events.

The study was initiated sequentially in the US, then Europe, and finally Japan, between 1996 and 1999. The sample analysed included black and white patients in the US ($n=5982$) and Europe ($n=3732$) with baseline data for BMI. Because of the small number of events in Japan-DOPPS to date, and because of prior observations of different BMI–mortality relationships in Asian American dialysis patients, these groups were excluded. A small number of patients known to be HIV positive or those with a diagnosis of AIDS ($n=81$) were excluded from the analysis to avoid the possibility that this group might unduly influence mortality risk estimates for lower BMI patients.

Analyses

BMI was measured as an individual's dry weight at study entry (kg), divided by the square of height in meters. There were over 8806 patient-years of follow-up from the US, plus 4214 patient-years from Europe. A total of 2580 deaths (2026 in the US and 554 in Europe) were observed in this sample (data collected through September 2000). Univariate statistics were computed for all of the predictor variables used in

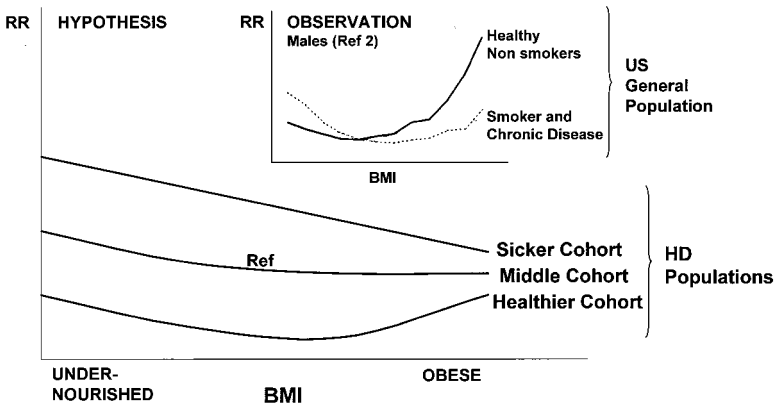

Fig. 1. Observation: the insert shows the pattern of the relationship between BMI and mortality relative risk (RR) in the general population for healthy non-smoking males and for male smokers with comorbidity (adapted from Ref. [2]). The plots for healthy non-smokers and for smokers with chronic disease appear superimposed because each patient group had its own group-specific reference category. Hypothesis: the shape of the relationship between BMI and mortality in HD-treated patients may also vary dependent on health status, as shown for three illness categories. In these analyses all patients will be compared with a single middle group BMI reference category, thus highlighting the difference in RRs between patient groups.

the survival analyses both for the overall study population and for specific HD patient subgroups. PROC GLM or Logistic regression (SAS 8.0) was used to compare baseline measurements of continuous variables and comorbidity prevalence between patient groups.

Survival was analysed as time from patient entry into the study to patient death, using multivariate Cox proportional hazards regression [8]. Patients were censored from contributing additional survival data to the analyses following a switch in treatment modality to peritoneal dialysis ($n=274$) or transplantation ($n=683$) or following change to a non-DOPPS HD facility (loss to follow-up) ($n=1757$), or at the time of the last round of data collection for a given facility, whichever came first. To account for differences in the duration of treated ESRD at study entry, all survival models were left-truncated [9]. All analyses were adjusted for independent country-effects (by stratification), and for age, gender, race, and smoking status. Models were also adjusted for serum albumin and for each of the comorbidity indicators listed in Table 1 (unless otherwise stated).

The World Health Organization (WHO) and the International Obesity Task Force propose the following grading system defining overweight and obesity based on BMI: overweight, BMI 25–29.9 kg/m^2; grade I or mild obesity, BMI 30–34.9 kg/m^2; grade II or moderate obesity, BMI 35–39.9 kg/m^2; grade III or severe obesity, BMI $\geqslant 40$ kg/m^2 [10,11]. This definition of overweight and obesity is used throughout the manuscript. In these analyses, BMI (kg/m^2) was primarily modelled as a categorical variable in five groups: BMI <20; 20 to <23; 23 to <25; 25 to <30; and $\geqslant 30$. The upper two categories were chosen to correspond to the WHO definition of overweight (25–30 kg/m^2) and obese ($\geqslant 30$ kg/m^2) [10]. In addition, a natural log transformation of BMI (lnBMI) was used to model linear correlations of mortality with BMI. The transformed BMI covariate, lnBMI, is normally distributed and it better approximates the levelling off in decreased mortality risk, which occurs at the higher extreme of body size. Initial survival analyses explored BMI–mortality relationships for the European and US data separately. Different effects of BMI on mortality risk were also sought for race and gender subgroups.

Subsequently the data were combined to facilitate analysis of BMI–mortality relationships in a number of healthier and sicker patient subgroups. The relationship between mortality and BMI was examined both between, and within, a sickest, a healthiest, and a middle tertile severity of illness group.

Table 1. Baseline patient characteristics for overall sample and for severity of illness subgroups

Variable (mean ± SD or per cent)	US and European DOPPS ($n=9714$)	Healthiest tertile	Middle tertile	Sickest tertile
Demographics and laboratory				
Age, years	61 (15)	55 (17)	62 (15)	66 (13)
Race (% black)	23	24	23	22
Gender (% male)	57	59	56	55
Vintage, years	2.9 (4.5)	3.5 (4.9)	2.9 (4.4)	2.2 (3.9)
Serum albumin, g/dl	3.7 (0.6)	4.0 (0.4)	3.7 (0.5)	3.3 (0.6)
BMI				
Mean BMI, kg/m^2	25.0 (5.3)	24.7 (5.0)	25.1 (5.4)	25.0 (5.5)
BMI subgroups (%)				
BMI <20	15.8	15.5	14.7	17.3
$20<$ BMI <23	25.0	26.1	24.7	24.3
$23<$ BMI <25	16.9	17.8	17.1	15.9
$25<$ BMI <30	26.2	26.7	26.3	25.5
$30<$ BMI	16.1	14	17.2	17.1
Comorbid conditions[a] *(% yes)*				
Coronary heart disease	43	14	42	73
Congestive heart failure	39	10	36	70
Cardiac, other[b]	35	16	34	55
Hypertension[g]	81	86	79	79
Peripheral vascular disease[c]	25	6	21	49
Recurrent cellulitis or gangrene	8	0	3	22
Cerebrovascular disease	17	5	14	32
Diabetes	38	14	39	60
Pulmonary disease[d]	13	3	10	27
Dyspnea[e]	30	5	25	59
Smoking	39	36	38	44
Cancer (other than skin)	11	4	11	17
Gastrointestinal bleeding[f]	8	2	6	16
Neurologic disease	9	2	7	19
Psychiatric disorder	25	9	22	44

[a]Medical history on or any time before date of study enrolment.
[b]Includes pericarditis; valvular heart disease; permanent pacemaker; and any arrythmia history.
[c]Includes history of claudication, rest pain, amputation, diagnosis of aortic aneurysm; history of aortic, and/or peripheral arterial bypass surgery.
[d]Chronic obstructive pulmonary disease or use of home oxygen.
[e]At rest or with minimal exertion (other than with excessive interdialytic weight gain).
[f]Within 12 months.
[g]Diagnosis of hypertension in medical record.

Patients were categorized into these groups using a comorbidity score derived from a Cox analysis of the entire study population, which determined regression coefficients that corresponded to independent mortality risks associated with serum albumin and with each comorbidity variable listed in Table 1. By summing the coefficients that corresponded to each individual's serum albumin concentration and comorbidity profile a continuous numeric score of severity of illness was generated at the patient-level.

A variety of additional analyses were also performed. BMI–mortality relationships were determined separately for age groups (age <45; age 45–60; age >60); smokers (defined as any current or former history of smoking) and non-smokers; diabetics and non diabetics; patients with or without documented vascular disease; and for patients who were both <45 years old and in the healthiest comorbidity tertile. The higher range of BMI was modelled in categories corresponding with mild obesity, BMI 30–34.9 kg/m^2 ($n=1055$); moderate obesity, BMI 35–39.9 kg/m^2 ($n=355$); and severe obesity, BMI $\geqslant 40$ kg/m^2 ($n=153$). Analyses were performed with and without adjustment for vascular diseases, diabetes, dialysis dose, dialysis treatment time, pre-dialysis serum creatinine, and nPCR to investigate whether these adjustments might alter the conclusions of the study. All analyses used the SAS Statistical Software System version 8.0. Statistical significance is reported at a P-value of 0.05.

Results

Bivariate analyses

Baseline patient characteristics at entry into DOPPS are shown in Table 1 for the overall study population and for the three major comorbidity groups. Differences in mean BMI and in the percentage of black patients were not clinically significant between the severity of illness subgroups. There were slightly fewer female patients in the healthiest patient group ($P=0.014$). The serum albumin concentration and all other demographic and comorbidity covariates were significantly different between the severity of illness subgroups ($P<0.0001$). Age and prevalence of each of the comorbidities (excepting hypertension) increased from the healthiest to the sickest comorbidity tertiles ($P<0.0001$). Duration of ESRD treatment in years at study start, 'vintage', and serum albumin concentration decreased from the healthiest to the sickest comorbidity tertiles ($P<0.0001$).

From the lowest to the highest BMI groups, mean pre-dialysis creatinine concentration increased, nPCR decreased and mean albumin concentration was relatively unchanged (Table 2). Delivered dialysis dose decreased with increasing BMI, despite a significant trend towards longer dialysis treatment times for patients with higher BMI. The crude mortality rate decreased from 26.9 deaths per 100 patient-years in the BMI <20 group, to 14.1 deaths per 100 patient-years for the BMI $\geqslant 30$ group (Table 2).

Multivariate analyses

Simultaneously adjusting for all of the factors shown in Table 1, the mortality risk decreased as BMI increased in both the US and Europe samples (Figure 2). A significant inverse linear correlation of relative mortality risk (RR) with ln(BMI) was found in both samples ($P<0.0001$). In both the US and Europe, overall mortality risk was significantly lower for BMI $\geqslant 30$ as compared with the reference BMI group 23–24.9 (US RR 0.77, $P=0.002$; Europe RR 0.61, $P=0.01$). The patterns are not significantly different for the US and Europe.

Adjusted mortality risk also decreased as BMI increased in both black and white patients (inverse linear correlation with ln(BMI), $P<0.0001$). In black and white patients the lowest mortality risk was again found for the BMI $\geqslant 30$ category (Table 3). Similar significant results were seen when BMI was modelled separately by gender, as a log–linear and as a categorical variable. Statistical and/or clinical evidence for an interaction in determining mortality risk between continent, race, or gender and BMI was lacking. Therefore, the US and Europe samples were combined in subsequent analyses.

Figure 3 shows the relationships between adjusted relative mortality risk (plotted on a log scale) and BMI, for HD patient populations that differed in terms

Table 2. Laboratory and dialysis variables and unadjusted death rates across BMI subgroups

Variable (Mean $\pm$ SD or per cent)	BMI (kg/m^2)				
	<20	20–22.9	23–24.9	25–29.9	$\geqslant 30$
Albumin (g/dl)	3.6 (0.6)	3.7 (0.6)	3.7 (0.6)	3.7 (0.6)	3.6 (0.5)
Creatinine (mg/dl)	8.1 (3.3)	8.7 (3.5)	8.9 (3.6)	8.9 (3.5)	9.2 (3.7)
nPCR (g/kg/day)	1.06 (0.28)	1.05 (0.27)	1.03 (0.26)	1.04 (0.26)	1.0 (0.24)
sp Kt/V[a]	1.51 (0.31)	1.42 (0.29)	1.4 (0.29)	1.35 (0.26)	1.29 (0.27)
D.[b] Time $\leqslant 3$ h (% of patients)	41	36	32	32	27
$3<$ D.[b] Time $\leqslant 4$ h (% of patients)	53	58	61	59	60
D.[b] Time >4 h (% of patients)	6	6	8	9	12
Deaths per 100 patient-years	26.9	22.2	19.6	17.4	14.1

[a]Single-pool Kt/V.
[b]Prescribed dialysis treatment time.

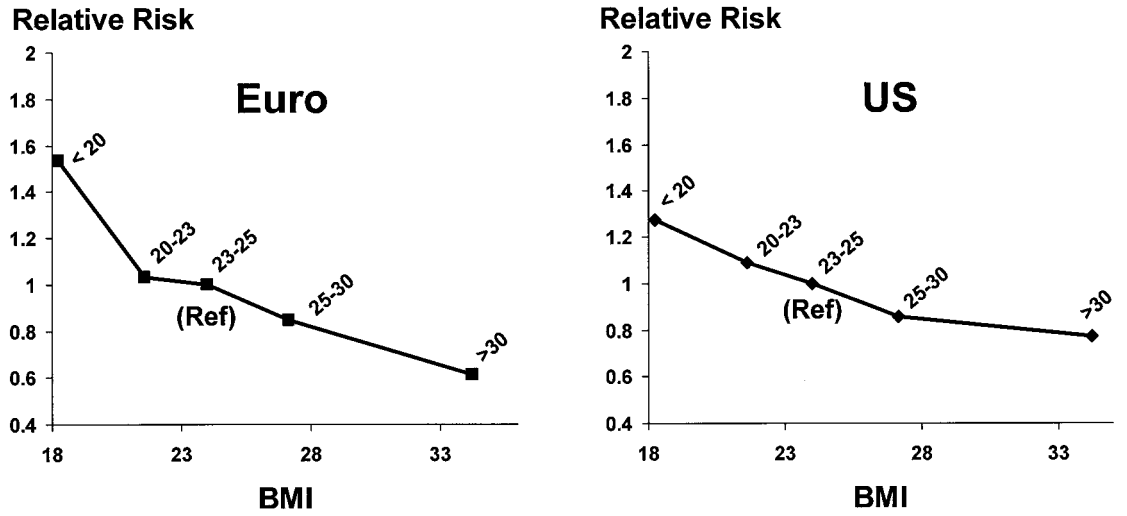

Fig. 2. Relative mortality risk *vs* BMI, US and Europe. BMI points from categorical analysis are plotted at the average BMI for each group. Mortality risk decreases as BMI increases. An inverse linear relationship between mortality and lnBMI is significant for both the US and Europe ($P<0.0001$). Adjusted for demographics, all comorbid conditions listed in Table 1 and albumin.

Table 3. Relative mortality risk (RR)[a] for body mass index in HD patient subgroups

	BMI (kg/m^2)				
	<20	20–22.9	23–24.9	25–29.9	⩾30
RR by race					
White ($n=7474$)	1.31[b]	1.11	1.00	0.80	0.66[c,d]
Black ($n=2240$)	0.88[b]	0.67	0.69	0.63	0.45[c,d]
RR by severity of illness					
High ($n=3205$)	2.24[b]	1.87	1.74	1.46	1.40[c]
Moderate ($n=3271$)	1.33[b]	1.05	1(ref)	0.79	0.61[c,d]
Low ($n=3238$)	0.70[b]	0.59	0.44	0.48	0.36[c]
RR by age group					
⩾65 ($n=4427$)	2.23[b]	1.81	1.70	1.33	1.11[c]
45–64 ($n=3858$)	1.32[b]	1.13	1(ref)	0.91	0.76[c]
<45 ($n=1704$)	0.80	0.57	0.53	0.57	0.52
RR by smoking status					
Current/former ($n=3821$)	1.53[b]	1.28	1(ref)	0.94	0.92
Never ($n=5893$)	1.40[b]	1.08	1.06	0.87	0.73[c,d]
RR by diabetes					
Diabetic ($n=3707$)	1.37[b]	1.06	1(ref)	0.87	0.81[c]
Non-diabetic ($n=6007$)	1.11[b]	0.93	0.88	0.71	0.54[c,d]
RR for combined subgroup					
Age <45 and low					
Severity of illness ($n=935$)	1.53	1.03	1(ref)	0.90	0.87

[a]Adjusted for demographics, comorbidity, and duration of ESRD.
[b]Significantly greater than RR for subgroup-specific BMI 23–24.9 category ($P<0.05$).
[c]Significantly lower than RR for subgroup-specific BMI 23–24.9 category ($P<0.05$).
[d]Significantly lower than RR for subgroup-specific BMI 25–29.9 category ($P<0.05$).

of overall health status at the start of the study as defined by severity of illness tertiles (Table 1). The log scale facilitates direct comparison of the slope, or rate of change, in mortality risk between different patient subgroups as BMI increases. Mortality risk is seen to increase from the healthiest to the sickest comorbidity tertile. This further confirms the successful stratification of patients by overall health status. The decrease in mortality risk with increasing BMI in each comorbidity tertile was statistically significant (inverse linear correlation with ln(BMI), $P<0.0001$). Despite stratification on health status no upturn in mortality risk was detected for overweight and/or obese patients.

HD subpopulations were also defined, respectively, by age and by smoking history. A predicted separation

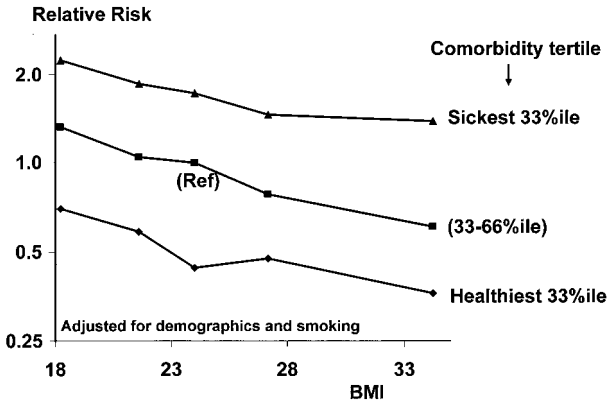

Fig. 3. Relative mortality risk *vs* BMI, for sicker and healthier HD patient subgroups (US and Europe). BMI points from categorical analysis are plotted at the average BMI for each patient cohort. Tertiles of a linear indicator of severity of illness define the three patient cohorts. In each cohort mortality risk was highest for BMI <20 and lowest for BMI $\geqslant 30$ (inverse linear relationship with ln(BMI), $P<0.0001$).

in adjusted mortality risk for increasing age and smoking status was found across all but one BMI category (Table 3). The continuous variable, ln(BMI), correlated inversely with mortality risk, at a *P*-value <0.007, in each patient group. There was no evidence for an elevated mortality risk for overweight or obesity in these patient subgroups.

Table 3 shows BMI–mortality relative mortality risk estimates derived from modelling BMI as a categorical variable for a variety of HD patient subpopulations. Within all patient subgroups, the highest adjusted mortality risk was found for BMI <20, as compared with BMI 23–24.9 (significant at $P<0.05$, except for the two groups with the smallest numbers of patients and events). Within all patient subgroups (Table 2), the lowest adjusted mortality risk was found for BMI $\geqslant 30$. Comparisons within 10 of the 13 subgroups found that the mortality risk ratio for BMI $\geqslant 30$ was significantly less than the risk ratio for BMI 23–24.9 ($P<0.05$). In blacks, whites, non-smokers, non-diabetics, and patients in the middle tertile group for severity of illness, the mortality risk ratio for the obese group (BMI $\geqslant 30$) was significantly less than the risk ratio for the overweight group (BMI 25–29.9, $P<0.05$). Similar trends in relative mortality risk with increasing BMI, albeit not statistically significant, were found for the two subgroups with the smallest numbers of patients and patient deaths (patients <45 years old at study entry and patients from this age group who were also in the lowest severity of illness score tertile).

To further investigate the relationship between high BMI and mortality, the upper range of BMI for the entire DOPPS sample was modelled in categories corresponding with overweight, mild, moderate, and severe obesity. As compared with a 'normal' BMI reference group (BMI 23–24.9) significantly lower adjusted mortality risks were found for overweight (RR 0.84, $P=0.008$), mild obesity (RR 0.73, $P=0.0003$), and moderate obesity (RR 0.76, $P=0.02$). In comparing the 153 patients with BMI in the severe obesity range to this reference group, a relative mortality risk of 0.83 was found ($P=0.331$). As compared with an overweight reference group (BMI 25–29.9), mild obesity (BMI 30–34.9) was associated with a decrease in mortality risk that was borderline significant ($P=0.08$). No other comparisons of mortality risk within the overweight, mild, moderate, and severe obesity categories produced statistically significant differences.

Analyses performed without adjustments for vascular diseases and diabetes did not alter the results of the study. Neither adjustment for dose of dialysis and duration of dialysis, or for pre-dialysis serum creatinine and nPCR, were found to significantly alter the association between BMI and mortality.

Discussion

BMI is a simple, cheap and easy to calculate standardized measure of body size. It is widely used in epidemiologic research to define both a normal range for body size and a grading of overweight and obesity [10,11]. In the US, HD patients have lower BMIs as compared with age- and sex-matched controls in random surveys of the general population [2,4]. The prevalence of protein-calorie malnutrition in HD patients in Spain was estimated at 52% in men and 46% in women [12]. Estimates from other sources in Europe also corroborate findings of a high prevalence of protein-calorie malnutrition and body fat depletion [13].

In the US, irrespective of the measurement (BMI, per cent ideal body weight, or weight-for-height percentiles), several investigators have found a significant inverse relationship between mortality risk and body size in HD populations [2–5,14]. Less has been published relating BMI to mortality for HD patients in Europe. A decrease in mortality risk with increasing BMI was reported for a population of mostly young, non-diabetic patients treated with maintenance HD in France during the 1970s [15]. The present study extends prior observations by finding that higher BMI is associated with improved survival in a representative sample drawn from contemporary HD patients in the US and five European countries.

We were also interested in a new hypothesis, namely, whether overweight might be associated with an increased mortality risk within 'healthier', as compared with 'sicker' HD patient populations. Observations both in the general population and in a subpopulation of ESRD patients in the US suggested the possibility of such effect modification by health status/severity of illness burden [5,6]. To investigate this hypothesis BMI–mortality relationships were defined for a variety of patient subgroups. In one approach we used the data on patient-level comorbidity, serum albumin

concentration and survival to describe three equal-sized severity-of-illness groups (tertiles). Patients received a score based on their individual comorbidity profile and serum albumin concentration (methods). This approach worked well to divide the total study population into strata, which were characterized by a gradient of increasing comorbidity prevalence and worsening survival as one moved from the 'healthiest' to the 'sickest' group (Tables 1 and 3). Contrary to the hypothesis, a survival benefit was found for overweight patients (BMI 25–29.9), which was improved upon in the obese patient category (BMI $\geqslant 30$) across the healthier, as well as the sicker, groups of HD-treated patients. Even within a cohort of <45 year old patients with low comorbidity overweight/obesity was not associated with decreased survival.

Increasing dialysis dose correlates with improved survival in high and low BMI patients. However, delivered dialysis dose tends on average to be lower in large people. In contrast, dialysis treatment times are found to be longer in large people. Recently, the critical importance of adjusting for confounding effects of body size when describing the effects of dialysis dose on mortality has been highlighted [16,17]. For the primary analyses presented in this paper we deliberately choose not to adjust for dialysis dose. This approach was taken because lower dialysis dose is a plausible mechanism through which increasing BMI might be harmful for HD patients [18]. However, dose was adjusted for in sensitivity analyses and this did not significantly alter the results. Similarly, the primary analysis did not adjust for dialysis treatment time. It might be hypothesized that increased prescription of longer treatment times could favour improved survival for larger patients. However, adjustments for treatment time with or without dose adjustment did not change the direction or magnitude of the BMI associations with mortality. Similarly, the shape of the BMI–mortality associations was also unaffected by whether or not adjustments were made for vascular comorbidities and diabetes.

The present study included a large number of patients and a large number of events. Nonetheless, the average follow-up time per patient is relatively short, 1.34 ± 0.95 years. It might be argued that insufficient time had accrued for individuals to suffer adverse consequences of their higher body size in this study. Yet in a previous population-based study in HD patients higher BMI, in prevalent or incident HD patients, was shown to confer a survival advantage even as late as 5 years after the date of measurement [2]. Furthermore, cross-sectional studies in the US and Europe have found that body size is significantly lower the longer patients have been on dialysis prior to the time of survey sampling [13,19]. Thus, for the average prevalent patient receiving HD treatment and entering a study, higher body size is not likely to have developed just prior to study start while receiving HD treatment. Instead higher BMI most likely predates by a significant length of time the study start date, and for many may have been present close to or even well before the time of diagnosis of ESRD. Both this assumption and a particular statistical technique, which was used for survival analysis in this paper, namely left-truncation [9], address some of the concerns regarding duration of follow-up. A left-truncated survival analysis allows patients to inform survival for the period of their ESRD life history that is followed in the study. This is dependent on their duration of ESRD at study start date. The mean duration of ESRD at study start was 2.9 ± 4.5 years (95% of the population fall between 0 and 12.5 years of ESRD). With left-truncation, a survival analysis is produced that covers the duration of ESRD life history provided for by the patients in this study. In a left-truncated model an average of 1 year of follow-up for 100 patients, with different duration of ESRD, can be as informative as 10 years of follow-up per patient for 10 patients.

Large numbers of patients meet the WHO guidelines for overweight (BMI 25–30, $n=2541$) and mild (grade I) obesity (BMI 30–35, $n=1054$). A smaller number met definitions for moderate (BMI 35–40, $n=355$) and severe (BMI >40, $n=153$) obesity. The major analyses grouped all patients with BMI >30 kg/m^2 together. In an additional analysis using the entire study population, we subdivided obese patients into the above three grades of obesity. The severe obesity group had a slightly higher mortality than the mild to moderate obesity group but the difference was small and far from statistically significant. Although the relative mortality risk appears to level off for BMI subgroups beyond mild obesity, either an advantage or a disadvantage in terms of survival for individuals at the margins of the data (extremes of body size) could be missed because of a lack of power. However, a precise estimate of mortality risk is provided for BMI groups corresponding to overweight and grade I obesity, for whom in the general population, but not apparently the ESRD population, adverse health events are substantially increased, all else equal [6].

The explanations for the marked differences in mortality risk patterns by BMI ranges within the HD population *vs* the general population are not known. Although higher BMI correlates with increased body fat mass, and hence increased energy reserve, it is not a perfect correlate. For instance, BMI cannot differentiate a weight change that is due to an increase in muscle-mass from that due to an increase in fat-mass or that due to increased water weight. In this study, the shape of the BMI mortality relationship was unchanged in a sensitivity analysis, which simultaneously adjusted for other measures that might separately characterize fat-free mass. These measures included height (a surrogate for stature), pre-dialysis creatinine (a surrogate for muscle mass), plus/minus regression derived estimates of body water. Therefore, at least some of the benefits of higher BMI in HD patients may accrue from improved nutritional status. Perhaps patients with increased nutritional reserves on HD are better able to withstand the

cumulative stresses over time of insufficient protein-calorie intakes, inflammation, chronic acidosis, infections, vascular access failures, hospitalizations and suboptimal small- and middle-molecule solute clearances.

Survival effects in higher BMI individuals may outweigh the harmful effects of being overweight or obese on cardiovascular disease. Perhaps other causes of accelerated atherosclerosis, characteristic of the uraemic milieu, drive vascular disease in all HD patients, rendering the traditional independent risk factor overweight/obesity relatively less important [20]. Alternately, suboptimal nutrient intake may combine with other processes such as inflammation to promote accelerated vascular disease and malnutrition [20]. Lastly, it is also important to recognize that patient selection may play a role in the observed results. Although the analyses adjust for the presence of a wide range of comorbidities, data characterizing severity of disease (for example, severity of cardiovascular disease) are limited. If a non-random distribution of disease severity were to exist across BMI groups, this could impact the shape of the association between BMI and mortality.

The strengths of this paper are founded in the design of the DOPPS study. Attention to representative sampling within countries, and the ongoing prospective subject enrolment starting in 1996, makes the results relevant to current HD populations across the US and five European countries. Detailed data collection allowed adjustment for demographics and comorbidities and multiple approaches to testing the hypothesis. The large sample size and large number of observed events provided power to characterize important relationships with precision. The magnitude of the differences in survival across BMI groups (Table 2) emphasizes the clinical significance of the results. The statistical methodologies employed multivariate survival analyses with multiple adjustments for confounding and for duration of ESRD. Finally, multiple supplemental analyses of the effects of comorbidity adjustments, dialysis dose adjustments, and BMI cutpoints were also performed to enhance the validity of the study.

This study defines the consistency of the association of mortality with BMI in HD populations. It cannot, however, provide causal inference. Although increasing body size correlates significantly with a decreased mortality risk for patients with ESRD on HD, it will require further study to determine if an intervention, which promotes higher BMI, or prevents a reduction in weight (and thus BMI), can improve survival. Potentially modifiable exposures including smoking, vascular access type, dialyser and reuse practices, anaemia, dietary protein intake and delivered dialysis dose have been shown to correlate with serum albumin concentrations [21]. Initially, there is a need to identify those factors that are independently associated with BMI and or changes in BMI in dialysis patients. If these identified factors are amenable to intervention then the present study supports testing hypotheses that such interventions could improve survival in HD patients.

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