Obesity in Hemodialysis Patients: Is it an Innocent Phenomenon?

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Introduction

In 1972, Keys and co workers introduced the body mass index (BMI) as a weight for height relationship to be used as a useful indicator for body fatness (1). Later, the great concern about the importance of obesity has appeared, as many epidemiologic studies have shown that obesity is associated with higher rates of hypertension, diabetes, cardiovascular disease and premature death in general population (2). The implications of BMI in maintenance hemodialysis (HD) patients are unclear. Paradoxical to normal population the majority of the studies up to date have found a positive association between the BMI and survival on HD patients. Intrestingly, among renal transplant recipients, obesity either at the time of or after renal transplantation appears to be associated with shortened patient survival (3, 4). Similarly existence of any relationship between survival and BMI in peritoneal dialysis patients is not clear at the present time like patients with chronic renal disease not on any renal replacement therapy (5).

Possible mechanisms underlying the obesity associated survival advantage remain unknown. Existence of better nutrition may be an explanation. The unique patterns of malnutrition in the end stage renal disease population may account for the paradoxical association of obesity with a lower risk of mortality. In relation to this, Glanton and co workers found the protective effect of obesity was due to its lower association with other comorbid factors which contribute to a state of malnutrition (6). So they developed their hypothesis stating that obese patients may have effectively already been selected out as patients who had not yet developed serious comorbidity at the time of presentation to ESRD.

There are a lot of cardiovascular risk factors in HD patients leading to accelerated atherosclerosis like inflammation, hyperhomocysteinemia and hypertension. While there were some growing evidence about association of obesity and better survival, it should be helpful to seek about the relationship between BMI and cardiovascular risk factors in HD patients to find out a plausible mechanism of obesity associated survival advantage.

Patients and Methods

We analyzed the association of BMI and other anthropometric measures with common cardiovascular risk factors and serum indices of nutritional status in 83 adult patients (45 male and 38 female) on maintenance HD thrice weekly. Their average age was 48±14 years and duration of HD was 73±16 months. To avoid possible confounding results all patients who had ever received a renal transplant, or in active infectious disease state or having malignant disorder were not included. Ten patients (3 male, 7 female) with BMI under 18.5 kg/m^2 were also excluded from the study later as over expression of malnutrition might affect the results. Analysis of variables was done on the results of remaining 73 patients with BMI greater than 18.5 kg/m^2.

BMI, triceps skin fold thickness (TST), midarm muscle circumference (MAMC), waist circumference (WC) and hip circumference (HC) were measured as anthropometric variables. The BMI was calculated as dry weight in kilograms divided by the square of height in meters. Anthropometric measurements were done as described earlier (7). Clinical data for C-Reactive protein (CRP), homocysteine, lipids (total cholesterol, LDL-cholesterol, triglyceride, and HDL-cholesterol), apolipoproteins (lipoprotein a, apolipoprotein A1 and apolipoprotein B100), albumin and prealbumin were collected from the medical records of preceding 6 months for each individual patient. In all subjects, an ultrasound high-resolution B-Mode imaging examination of the common carotid arteries (CCA) for the measurement of of the intima media thickness (IMT) was done. Determination of blood pressure control was done by 24-hour ambulatory blood pressure (ABP) monitoring devices and records were used for analysis.

Statistical analysis

Results were expressed as mean±SD. Differences in continuous variables among groups were examined by a nonparametric test (Wilcoxon-Rank Sum test). To determine the correlations between variables Pearsons' test was used. All statistic analyses were conducted using the SPSS software program. A p value of less than 0.05 was considered to denote statistical significance.

Results

According to BMI 52 patients were classified as normal while 21 patients were overweight and obese. Classification was based on international BMI cut off values: Obese>30 kg/m^2, overweight=25 to 29.9 kg/m^2, normal=18.5 to 24.9 kg/m^2 and underweight< 18.5 kg/m^2. As a result of small sample size and relative rare frequency of obesity in our population, patients in the category of obese and overweight were simply called as obese altogether as otherwise over

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normal for BMI. Table-1 lists the demographic information of normal and obese patients.

Table-1. Demographic information of patients

Parameter	All patients	Normal	Obese	P
N	73	52	21	>0.05
BMI	22.9±3.68	21.16±1.8	28.34±2.3	<0.01
Gender (female/male)	31/42	23/29	8/13	>0.05
Age (years)	49±13	46±12	57±10	<0.05
HD duration (months)	74±18	78±12	64±18	>0.05
Hypertension	20/73	14/52	6/21	>0.05
Smoke	12/73	9/52	3/21	>0.05
Diabetes	9/73	6/52	3/21	>0.05
Hepatitis C positivity	27/73	25/52	12/21	>0.05
Hemoglobin (g/dl)	10.5±1.7	10.5±1.6	10.8±2.0	>0.05
Creatinine (mg/dl)	11.0±2.7	11.2±2.6	10.6±3.0	>0.05

There were some correlations between anthropometric measures and cardiovascular disease risk factors. HC was positively correlated with total cholesterol (r=0.29, p<0.05), triglyceride (r=0.28, p<0.0.5) and apolipoprotein B100 (r=0.30, p<0.0) levels. WC and MAMC also found positively correlated with triglyceride (r=0.33, p<0.05 and r=0.24, p<0.05 respectively) and apolipoprotein B100 (r=0.33, p<0.01 and r=0.24, p<0.05 respectively) levels. TST was not in correlation with any of the parameters.
Results of 24-hour ABP recording of each patient were determined as mean values of systolic blood pressure, diastolic blood pressure, pulse pressure and heart rate during day time, night time and overall 24 hours separately. None of the parameters were different between normal and obese HD patients.
Evaluation of markers of inflammation, nutrition and lipids showed some significant differences according to the BMI. CCA IMT values also, as an indicator of atherosclerosis, also found different between normal and obese HD patients. Table-2 shows the differential values of cardiovascular risk factors between normal and obese patients.

Discussion

The underlying mechanisms resulting in better survival for obese HD patients is still unknown. Although large prospective studies like Framingham Hearth Study, indicates that increased body mass in itself is an independent risk factor for development of cardiovascular disease in normal population (8), the general trend in almost all epidemiological studies of maintenance HD patients has been consistent with the reverse epidemiology (6, 9). The reverse epidemiology or dialysis risk paradox is a new concept that should be further examined.

Table-2. Differential list of factors according to BMI of patients (mean±SD, Kruskal Wallis Test)

Parameter	All patients n=73	Normal n=52	Obese n=21	P
C-RP (mg/dl)	1.2±1.1	1.1±1.0	1.4±1.1	0.042
Homocysteine (mg/dl)	26.8±8.0	25.9±7.9	29.7±8.0	0.049
Total cholesterol (mg/dl)	160±37	156±39	171±27	>0.05
LDL-cholesterol (mg/dl)	91±34	89±37	99±23	>0.05
Triglyceride (mg/dl)	147±49	143±51	158±40	>0.05
HDL-cholesterol (mg/dl)	38±13	38±13	39±12	>0.05
Lipoprotein a (mg/dl)	23.9±18.7	24.5±19.3	21.8±16.9	>0.05
Apolipoprotein A1 (mg/dl)	104.9±18.2	104.6±18.7	105.9±16.8	>0.05
Apolipoprotein B100 (mg/dl)	76.3±20.9	73.3±21.0	86.5±17.6	0.017
Albumin (g/dl)	3.8±0.3	3.8±0.3	3.7±0.3	>0.05
Prealbumin (mg/dl)	31.8±7.6	30.5±7.4	36.3±6.7	0.006
CCA IMT (mm)	0.66±0.24	0.62±0.21	0.78±0.30	0.035
24-hr Systolic BP (mmHg)	118±22	117±20	120±28	>0.05
24-hr Diastolic BP (mmHg)	75±15	74±13	80±21	>0.05
24-hr Pulse Pressure (mmHg)	42±10	43±11	39±8	>0.05

However, the relationship between an increased BMI and a better clinical outcome in HD patients is not completely uniform. Glanton et al indicated that obesity was associated with increased risk of infectious death in female dialysis patients (6). Another study by Kaizu et al stated that a BMI of more than 23.0 showed lowered survival rates compared to patients with BMI of 17.0-18.9 (10). They provided one of the longest follow up periods, nearly 12 years in the early 1980s'. Thus, it is possible that obese patients may have better survival in the short, but not necessarily in the long term. These two studies are in agreement with that racial or gender differences may play a role as cofactor in BMI-survival relation in HD patients.
In addition, Aoyagi et al implicated the importance of age in BMI related reverse epidemiology (11). According to their results, dialysis risk paradox appears when patients are over age of 60 and BMI value associated with the lowest mortality rate is approximately 20 kg/m^2 for patients under 60 years of age. Similarly, mean age of patients in DOPPS is 60.8 years (9). Glanton et al also found one year survival was 82% for obese patients vs. 74% for non-obese patients with mean age of 62.8 years (6). In our study, mean age of patients was 49 years, significantly lower than other studies. Our results stating the association of cardiovascular risk factors with obesity may show inconsistent results if long term survival analysis done. Thus, as other authors said, reverse

epidemiology may not be true for young patients as the physical strength of aged people rather than youngs may be positively correlated with body fatness (11). Supporting this, Glanton and co workers found that the presence of major medical illness was strongly associated with non-obesity among 151.027 chronic dialysis patients (6). In their study prevalence of diabetes, hypertension and congestive heart failure were 44.2%, 24.0%, 35.0% respectively. In addition mean hematocrit of the patients was 26.5%, significantly lower than target value stated by Guidelines. Also in DOPPS, 49.1%, 84.8% and 47.1% prevalence of these comorbidities were present (9). On the other hand, prevalence of diabetes was much lower in our study (12.3%), while prevalence of hypertension was similar (27.3%). The mean hematocrit value of our study population was also in recommended limits (31.5%) for minimizing the effect of anemia on development of cardiovascular disease. As author suggest that some of the "protective" effect of obesity is due to its lower association with comorbidity, our results stated that in the absence of comorbid factors beneficial effects of obesity may not be present (6).

Longitudinal studies show that malnutrition is associated with a reduced life expectancy mainly because of cardiovascular and infectious complications. The clinical evidence of malnutrition includes decreased relative body weight, skin fold thickness, and arm muscle circumference (12). While reported annual mortality rates range from 23.6% in US, to 10.7% in Europe and to 9.5% in Japan, a common factor of increased death risk in these populations is malnutrition (13). Several factors are responsible for malnutrition of HD patients. Protein energy intake is often reduced because of inappropriate dietary restrictions, anorexia, and taste alterations, promoting malnutrition in most patients entering dialysis. A state of persistent catabolism may result from acidosis, resistance to anabolic factors such as growth hormone, insulin and insulin like growth factor-1, as well as chronic inflammatory state caused by dialysis membrane and fluid bioincompatibility (14). In addition losses of nutrients, including glucose, amino acids, proteins and vitamins, occur during dialysis treatment. In 1990, Lowrie and Lew showed that in over 12.000 maintenance HD patients followed for 12 months, of various predialysis serum chemistries, the serum albumin exhibited the most striking odds ratio for survival (15). As an indicator of malnutrition, low serum albumin is also frequently associated with low BMI which is an also independent indicator of malnutrition in turn. Consequently, previous studies may not conclude that the relation between obesity and survival advantage is free from the effect of nutritional status. We believe that exclusion of underweight patients (BMI<18.5 kg/m^2) from our study may help us to compare the association of cardiovascular disease risk factors solely with BMI as we eliminate the adverse effects of malnutrition.

Our study is retrospective in nature. Low rates of comorbid factors in our patients may indicate that there may be some selection bias. As other authors said, there might be beneficial effects of obesity on survival in our HD patients, but deaths of patients with low BMI and comorbid factors would cause the remaining of healthy patients for normal BMI group. According to our results, higher levels of cardiovascular disease risk factors and higher prevalence of atherosclerosis in obese patients is inconsistent finding with reverse epidemiology as stated before. Thus "the reversal of the reverse epidemiology" and a return to "traditional epidemiology" may be the result of this mentioned selection bias.

In conclusion, assessing the BMI of chronic HD patients may provide useful information about the future risk of mortality. According to the results of large epidemiologic studies, obesity seems to be associated with higher survival advantage for HD patients, although underlying mechanisms remains to be clarified. As the supporting studies are mainly observational in nature, in the absence of a cause and effect study, the linkage between obesity and survival could still be an association.

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