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Obesity Paradox in Patients on Maintenance Dialysis

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Abstract

Overweight (body mass index [BMI] = 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) have become mass phenomena with a pronounced upward trend in prevalence in most countries throughout the world and are associated with increased cardiovascular risk and poor survival. In patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis an 'obesity paradox' has been consistently reported, i.e., a high BMI is incrementally associated with better survival. While this 'reverse epidemiology' of obesity is relatively consistent in maintenance hemodialysis patients, studies in peritoneal dialysis patients have yielded mixed results. A similar obesity paradox has been described in patients with chronic heart failure as well as in 20 million members of other distinct medically 'at risk' populations in the USA. Possible causes of the reverse epidemiology of obesity include: (1) time-discrepancies between the competing risks for the adverse events that are associated with overnutrition and undernutrition; (2) sequestration of uremic toxins in adipose tissue; (3) selection of a gene pool favorable to longer survival in dialysis patients during the course of CKD progression, which eliminates over 95% of the CKD population before they commence maintenance dialysis therapy; (4) a more stable hemodynamic status; (5) alterations in circulating cytokines; (6) unique neurohormonal constellations; (7) endotoxin–lipoprotein interactions; and (8) reverse causation. Examining the causes and consequences of the obesity paradox in dialysis patients can improve our understanding of similar paradoxes observed both for other conventional risk factors in chronic dialysis patients, such as blood pressure and serum cholesterol, and in other populations, such as patients with heart failure, cancer or AIDS or geriatric populations.

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Introduction

Individuals with chronic kidney disease (CKD) stage 5 who undergo maintenance dialysis treatment have a high mortality rate, currently 20% per year in the USA and 10–15% in Europe [1]. This high mortality has not changed substantially in recent years despite many advances in dialysis techniques and patient care [2]. Cardiovascular disease is the main cause of death in dialysis patients [3]. The currently estimated chronic dialysis population of 350,000 patients in the USA grows constantly and fast, and is projected to reach over one-half million by 2010 and over one million by 2020 [2].

It was once believed that the traditional cardiovascular risk factors and/or conditions related to dialysis treatment and technique are the main causes of poor clinical outcome; however, recent randomized controlled trials including the 4D Trial [4] and the HEMO and ADEMEX studies [5, 6] failed to show an improvement of mortality by lowering serum cholesterol levels or by increasing dialysis dose, respectively. Hence, it is not unlikely that conditions other than the traditional risk factors are related to the enormous cardiovascular epidemic and high death rate in this population.

An increasing number of epidemiologic studies, based on analyses of large samples of dialysis patients and national databases, have indicated paradoxical and inverse associations between classical cardiovascular risk factors and mortality in dialysis patients [7, 8]. Indeed, a worse survival among dialysis patients has been observed with a *low*, rather than a high, body mass index (BMI) [9] or weight-for-height [10], blood pressure [11], and serum concentrations of cholesterol [12], homocysteine [13] and creatinine [14]. Even more ironically are findings indicating that *high* values of these risk factors are paradoxically protective and associated with improved survival. This phenomenon has been referred to as 'reverse epidemiology' [7] or 'altered risk factor pattern' [8]. These epidemiologic findings have contributed to the growing confusion and have left physicians with the ongoing dilemma as to whether or not to treat obesity, hypercholesterolemia, hypertension, or hyperhomocysteinemia in chronic dialysis patients [8]. Among the above-mentioned cardiovascular risk factors that are inversely associated with mortality, the so-called 'obesity paradox' has been the most consistent and most extensively studied [15, 16]. In this manuscript, the paradoxical predictability of mortality of measures of body size and several hypotheses that have been advanced to explain these paradoxes are reviewed critically.

Obesity in the General Population

In recent years, overweight (BMI = 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) have become mass phenomena with a pronounced upward trend in

prevalence in virtually all developed and developing countries [17, 18]. The prevalence of obesity has reached epidemic proportions in the USA: It ranged between 13 and 15% between 1960 and 1980 [19–21], but doubled to 23 and 31% during 1988–1994 and 1999–2000, respectively [17, 22]. Obesity is a strong risk factor for the development of diabetes mellitus, atherosclerotic cardiovascular disease, cancer and even CKD [23–26]. However, despite detrimental effects of being overweight, 'obese nations live paradoxically longer than ever' [18]. The increasing prevalence of obesity may be understood in the light of evolution, because energy metabolism is asymmetric with energy accumulation being the necessary condition of survival during 'hard times' [18]. According to this theory, this genetic characteristic, the so-called thrifty gene(s), was necessary for survival of humanity, because during the course of history there was never a long period of uninterrupted food abundance, whereas famines and other hardships occurred frequently. Therefore, fat accumulation, when food was available, meant survival at times of hardship. In contrast, the potential detrimental effects of overnutrition and overweight generally only became manifest at an older age to which most people did not live and therefore were not very relevant to survival [18]. The foregoing model may explain why in chronic disease states obesity confers survival advantages [27].

Obesity and Survival in Hemodialysis Patients

Obesity has recently been reported to be a risk factor of the CKD progression to stage 5 [26], although this epidemiologic observation may be severely confounded by a strong survival bias [28], especially because many CKD patients die before they reach stage 5 [29]. Maintenance hemodialysis (MHD) patients appear to have a lower BMI as compared with age- and sex-matched controls from the general population [30–32].

Most epidemiologic studies have shown an inverse association between larger body size and lower death risk in MHD patients, independent of other markers of nutritional status [15]. The Diaphane Collaborative Study [33] appears to be the first to report the association between low BMI and high death rate in a cohort (1972–1978) of 1,453 mostly nondiabetic French MHD patients, which was confirmed 15 years later by Leavey et al. [34] (3,607 MHD patients) using the United States Renal Data System (USRDS) database. Fleischmann et al. [35] identified for the first time the so-called 'obesity paradox', i.e., a significantly higher survival rate in overweight and obese MHD patients (BMI $\geq$ 27.5 kg/m^2) compared to those with a normal weight (BMI = 20–27.5 kg/m^2) and underweight (BMI $<$ 20 kg/m^2) [35]. Wolf et al. [36] (9,165 MHD patients) and Port et al. [37] (45,967 incident MHD patients)

reported similar paradoxical associations in the USRDS database. The *Dialysis Outcomes and Practice Patterns Study* (DOPPS) [38] (9,714 MHD patients in the USA and Western Europe from 1996 to 2000) confirmed an inverse BMI–mortality relationship in MHD subpopulations defined by continent, race, gender, tertiles of severity of illness and comorbid conditions. Glanton et al. [39] (151,027 incident dialysis patients from the USRDS) found that the obesity paradox was not uniform across different gender and race/ethnicity subgroups and was stronger in African-Americans. Johansen et al. [40] (418,055 maintenance dialysis patients in the USRDS data) found that even morbid obesity was associated with increased survival, except for in Asian-Americans. High BMI and Benn's index were also associated with a reduced risk of hospitalization. Survival rates based on estimates of adiposity and fat mass yielded similar results, and adjustments of body weights for differences in lean body mass did not substantially alter the paradoxical associations [40].

Some investigators have studied body size surrogates other than BMI. Kopple et al. [10] examined weight adjusted for height percentiles in 12,965 MHD patients from the Fresenius database and found that those patients with greater weight-for-height had lower mortality rates. Lowrie et al. [41] (43,334 MHD patients from the Fresenius database) examined body surface area and weight divided by height (wt/ht) in addition to the BMI. The log of risk decreased in rough linear fashion for weight, weight-for-height, and body surface area [41]. Beddhu et al. [42] (70,028 incident MHD patients in the USRDS database) used 24-hour urine creatinine excretion as a indicator of muscle mass and concluded that higher muscle mass was a stronger predictor of survival than was higher total body weight in heavy MHD patients. However, their data showed that obesity was associated with better survival within each fat/muscle category [42]. The inherent associations of urine creatinine with renal function, muscle mass and meat intake may restrict the generalizability of the foregoing conclusions [43].

Kalantar-Zadeh et al. [9] recently examined the effects of both absolute magnitude of BMI (using the time-dependent Cox model) and changes in BMI over time on all-cause and cardiovascular mortality in a 2-year nonconcurrent cohort of 54,535 MHD patients in the national database of the second largest dialysis care provider in the USA (DaVita, Inc.). They found that obesity, including morbid obesity (BMI $> 35\,kg/m^2$), was associated with survival advantages in virtually all subgroups of age, gender, race, dialysis vintage, serum albumin, and Kt/V (fig. 1). Moreover, they showed for the first time that independently of almost any BMI level, weight loss is associated with increased mortality, whereas weight gain confers survival advantages [9] (fig. 2). Finally, in another recent study, Kalantar-Zadeh et al. [44] measured total body fat directly in 535 MHD patients over 3.5 years and found that not only a lower

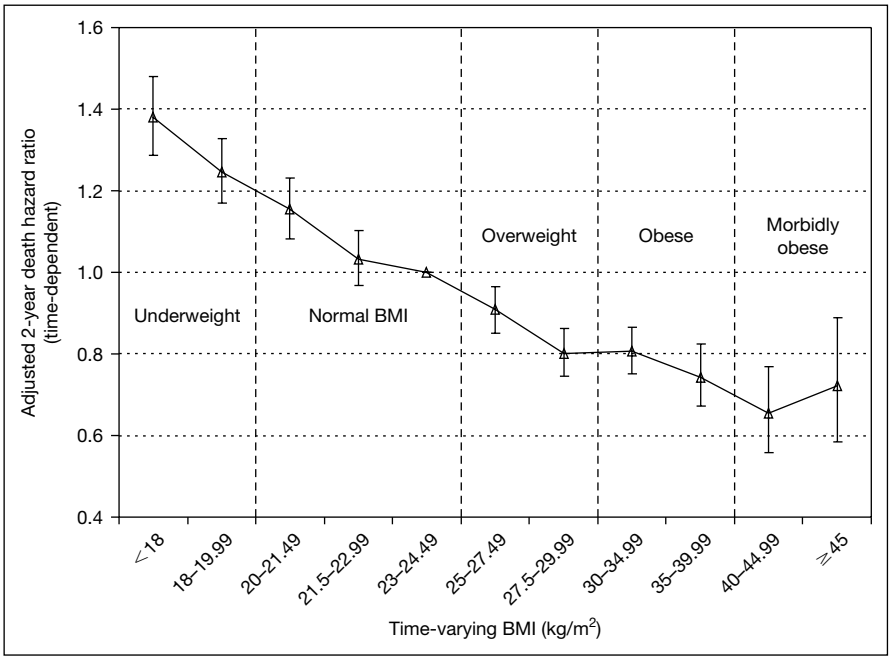

Fig. 1. Adjusted death hazard ratio in 54,535 MHD patients (7/2001–6/2003); recreated bases on data from reference [9].

total body fat was associated with higher mortality, but loss of body fat over time was associated with increased death risk.

Obesity and Survival in Peritoneal Dialysis Patients

Some [45–50], but not all [51–53], studies in chronic peritoneal dialysis (CPD) patients have reported inverse weight–mortality relationships [15]. In the CANUSA study, a 1% difference in the percent lean body mass was associated with a 3% change in the relative risk of death [45, 46]. McCusker et al. [47], Chung et al. [49], and Johnson et al. [48] found a significantly decreased survival rate in CPD patients with a lower body weight. The largest epidemiologic study of body weight and survival in CPD patients included nearly 46,000 CPD patients in 1990s [50], and showed that overweight and obese CPD patients had longer survival than those with normal BMI. These findings could not be adequately explained by lower rates of renal transplantation or lower technique survival rates. Abbott et al. [52] compared 1,675 MHD and 1,662 CPD patients and found that

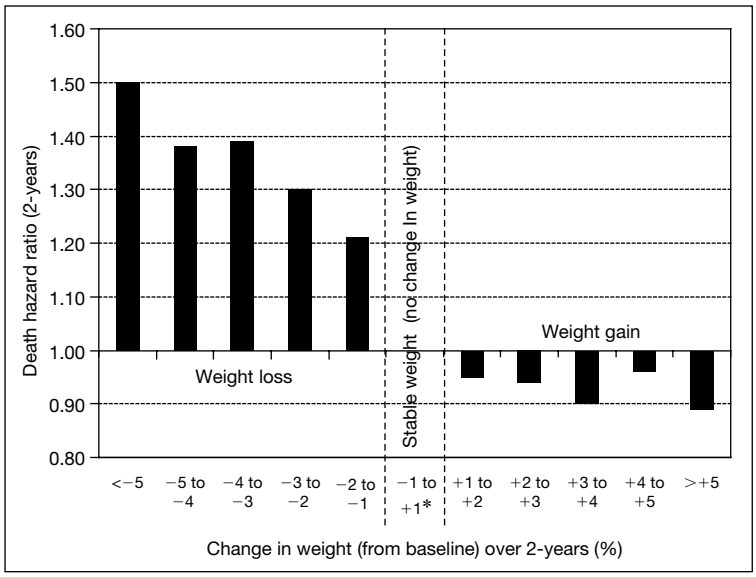

Fig. 2. Relative risk of death for changes in weight over time; recreated bases on data from reference [9].

5-year survival based on BMI cutoff of 30 kg/m^2 in CPD patients was not different than in MHD.

Several studies in CPD patients either have not found any survival advantage for obesity or have indicated a higher risk of death in obese CPD patients [53]. McDonald et al. [51] examined 9,679 CPD patients in Australia or New Zealand over an 11-year interval and found that obesity was independently associated with death and technique failure except among patients of New Zealand Maori/Pacific Islander origin. Stack et al. [54] examined CPD–MHD differences in a cohort of 134,728 new ESRD patients from the USRDS and concluded that the selection of HD over PD was associated with a survival advantage in patients with large body habits [54]. Beddhu et al. [42] hypothesized that the survival advantages of obesity is due to muscle mass both in MHD and CPD patients [55] using urinary creatinine as a indicator of muscle mass [56].

Other Populations with a Reverse Epidemiology

Patients with chronic heart failure (CHF) [57], geriatric populations [58], and patients with malignancy [59], AIDS [60], chronic obstructive pulmonary disease [61], or rheumatoid arthritis [62] also exhibit a risk factor reversal.

Table 1. Potential mechanisms that may result in the observed paradoxical associations between obesity and better survival in dialysis patients

Kidney Disease Wasting (Malnutrition–inflammation complex syndrome)
Time discrepancy between competitive risk factors: overnutrition vs. undernutrition
Unusual genetic constellation due to survival selection during CKD progression
Sequestration/storage of uremic toxins in fat tissue
Anti-inflammatory cytokines related to body mass, including adiponectins
Tumor necrosis factor alpha receptors
Endotoxin-lipoprotein hypothesis
Stability of hemodynamic status in obese patients
Neurohormonal alterations in obesity
Alteration of conventional risk factors in uremic milieu ('beyond Framingham')
Reverse causation
Survival bias

There appear to be at least 20 million Americans who may have a reverse epidemiology pattern [63]. There are striking similarities in the reported paradoxes between the patients with CHF, currently almost 5 million individuals in the USA, and MHD patients [64, 65]. Furthermore, millions of the fast-growing population of octogenarians and nonagenarians in the industrial countries appear to display a reverse epidemiology [63]. Studying the causal factors that engender the obesity paradox in chronic dialysis patients may confer better insight into understanding the pathophysiology and public health consequences of these phenomena in other populations.

Pathophysiology of the Obesity Paradox

Several hypotheses have been advanced to explain the obesity paradox in dialysis patients (table 1) [8, 15, 16]. Obesity and weight gain may be associated with a more stable short-term hemodynamic constellation and improved hemodynamic tolerance to afterload-reducing agents, especially because overweight and obese patients with heart failure tend to have higher systemic blood pressure values [66]. Thus, obese patients might better tolerate removal of large volumes of fluid during the hemodialysis procedure with less likelihood of hypotension. Obesity may mitigate stress responses and the heightened sympathetic and renin–angiotensin activity; the latter are associated with a poor prognosis in heart failure and fluid overload states such as in dialysis patients [67]. Hence, better outcome is expected if angiotensin axis can be blocked [68]. Altered cytokine and neuroendocrine profiles of obese patients may also play

a role in conferring survival advantages to obese patients. Adipose tissue produces adiponectins [69], as well as soluble tumor necrosis factor alpha receptors which may neutralize the adverse biologic effects of tumor necrosis factor alpha [70]. It is also possible, although not yet proven, that the uremic milieu or volume overload modifies the cardiovascular constellations so that factors 'beyond Framingham paradigms' are more relevant for survival [71].

It has been postulated that higher concentrations of total cholesterol (lipoproteins) are beneficial for dialysis and CHF patients, since a richer pool of lipoproteins can actively bind to and remove circulating endotoxins; hence, the increase pool of these lipoproteins may attenuate the propensity of endotoxins which would otherwise cause inflammation and subsequent atherosclerosis if unbound [72]. This so-called 'endotoxin–lipoprotein' hypothesis was originally advanced to explain the hypercholesterolemia paradox in CHF patients [73].

It is also possible that uremic toxins are more effectively sequestered when abundant adipose tissue is present. It has been shown that weight loss and reduction in adipose tissue is associated with the imminent release of and significant increase in circulating lipophilic hexachlorobenzene and other chlorinated hydrocarbons [74]. Weight loss may also be associated with reduced skeletal muscle oxidative metabolism, leading to a mitigated anti-oxidant defense [75]. These findings may provide one explanation for why body fat loss has recently been found to be associated with increased death risk in dialysis patients [44].

It is, of course, possible that BMI is not a cause but a consequence of conditions that lead to poor outcome in dialysis patients or in similar populations with a paradoxical risk factor profile. 'Reverse causation' is a known possible source of bias in epidemiologic studies that examine associations without the direction of the causal pathway [76]. Comoribid states may lead to kidney disease wasting or cardiac cachexia and also to higher rate of mortality. However, even if the reverse causation is a cause of the reverse epidemiology, it does not explain why obesity including morbid obesity is associated with better outcome than the traditional normal or healthy weights in dialysis patients.

Of the currently estimated 20 million individuals with CKD in the USA [77], it is projected that over 90% will die before advancing to end-stage renal disease [29]. Hence, only less than 5% of the large CKD pool will be the 'unlucky lucky' individuals to reach the dialysis facility chair [7]. This may lead to a significant 'survival selection' [64] resulting in genetic constellations in dialysis patients that may be significantly different than their early CKD predecessors [78]. According to this theory, those few CKD patients who reach ESRD may have either a more accelerated rate of progression of CKD or special genes that protected them against the fatal ravages of cardiovascular disease which is inherent to CKD. Whether this is called 'survival bias' or 'survival

selection' (similar to evolutionary natural selection), maintenance dialysis patients must be genetically or phenotypically dissimilar to their CKD predecessors who do not survive and may not have the survival characteristics and epidemiological features of their progenitors.

Survival advantages that exist in obese dialysis patients may, in the *short-term*, outweigh the harmful effects of these risk factors in causing cardiovascular disease and death in the *long-term* [7]. In other words, dialysis patients may not live long enough to die of the adverse effects of overnutrition, because they are more likely to die much faster of the consequences of undernutrition [64]. This so-called time-discrepancy between the two sets of competing risk factors, i.e., short-term killers (malnutrition–inflammation complex) vs. long-term killers (obesity and overnutrition), can explain why obesity treatment may be irrelevant or even harmful in many (but not all) dialysis patients if the issue at hand is the short-term survival. Currently 2/3 of all dialysis patients in the USA die within 5 years of commencing dialysis, a 5-year survival worse than many cancer patients [64]. Hence, treatment of malnutrition–inflammation complex, also known as kidney disease wasting, should be the target of efforts to improve survival in maintenance dialysis patients.

Conclusions and Future Steps

Studying the obesity paradox and other similar phenomena in dialysis patients leads to additional questions: Is the reverse epidemiology a true entity with clinical and public health implications in millions of patients with CKD, CHF, advanced age, malignancy, AIDS, etc., or is it a statistical fallacy that needs to be 'controlled away'? [79]. At which CKD stage does the reverse epidemiology start and in whom does it develop? Which groups of dialysis patients have a stronger, weaker or no obesity paradox? Can the so-called 'reversal of the reverse epidemiology' (or 'back-to normal) phenomenon upon successful renal transplantation of dialysis patients or with frequent (daily and/or nocturnal) dialysis treatment be confirmed? [64]. If this reversal of the altered risk factor relationships in these patients are real, what are the mechanisms for this phenomenon? What should be our therapeutic targets for body weight-for-height in our CKD and maintenance dialysis patients? Should we revise the current guidelines that recommend that obese dialysis patients on transplant waiting lists should lose weight as a prerequisite for renal transplantation? [40]. For that matter, what should be our therapeutic targets in maintenance dialysis patients for other clinical characteristics for which the usual risk factor relationships to mortality are altered, such as blood pressure or serum cholesterol or phosphorus, to mention a few? Is the evidence for these altered risk factor

relationships sufficiently established to justify proposing to research granting agencies, the funding of randomized, prospective interventional trials to examine the appropriate therapeutic targets for BMI or some of these other clinical targets in chronic dialysis patients?

The field of altered risk factor relationships is in its infancy and appears to be evolving quickly. It is possible that, in the long run, overweight patients, if they survive sufficiently long, will suffer from more cardiovascular consequences. Until more information is available, it is prudent to avoid causal inferences for such observational data.

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