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Cardiovascular Morbidity in Hemodialysis: The Reverse Epidemiology Phenomenon

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1. Introduction

The Framingham study that begun more than 60 years ago (1948) has shaped the way Western societies face cardiovascular disease (CVD). The relative impact of this study (now on its 3rd generation of participants) [1] has been so impressive that both public health authorities and the medical community have fully endorsed its results: since then, hypertension, dyslipidemia, tobacco smoking, diabetes mellitus and more recently obesity and hypertriglyceridemia are considered as the major risk factors for new cardiovascular morbidity and overall mortality.
Major advances aiming both at prevention and management have had a significant impact on survival of patients with CVD. These advances, together with the extinction of undernutrition after the 2nd World War, have led to an increase in survival and thus in the number of patients with chronic disease states (congestive heart failure, chronic kidney disease, dialysis patients, cancer etc) that survive over prolonged time periods. Numerous epidemiological studies over the last decade, have observed that in these subgroups of patients, the well established-for the general population- surrogates of cardiovascular risk and metabolic syndrome as obesity, hypercholesterolemia and hypertension are paradoxically associated with greater survival. Hence the term "reverse epidemiology paradox" was coined in medical literature.
Approximately 9% of the US adult population (about 20 million people) has chronic kidney d stage 1 (CKD-1) and 2% are receiving maintenance dialysis. It has been projected that dialysis patients will exceed 1 million by 2018. It should be emphasized that although dialysis for CKD-5 is expected to be life-prolonging, 5-year survival in the US is only about 35% for patients on dialysis [2,3]. Robust observational studies have repeatedly shown that even after adjustments for comorbidities, moderately higher levels of blood pressure, higher body mass index (BMI) and higher cholesterol levels are associated with improved survival.
This chapter will review data concerning the role of arterial hypertension, obesity, and cholesterol levels on cardiovascular morbidity and mortality in hemodialysis (HD) patients and discuss potential pathogenetic mechanisms that could possibly explain the so called "reverse epidemiology paradox".

2. Hypertension in dialysis: friend or foe?

The definition of arterial hypertension (AH) in the general population is based on observations showing a significant increase in cardiovascular morbidity and mortality over

a certain level of systolic and/or diastolic blood pressure (140/90 mmHg respectively). In the general population the association of hypertension with the occurrence of new CVE is indisputable [4-6] and even patients with high normal blood pressure have an increased cumulative incidence of CVE compared to normotensive subjects.

The same definition of AH (mainly pre-dialysis blood pressure) has been used for the dialysis population as well, although data concerning the impact of pre-dialysis hypertension on the occurrence of CVE and overall mortality show significant contradiction. Elevated BP may not represent the primary risk for overall survival in patients treated with hemodialysis; several studies have failed to show that high BP is an independent mortality risk factor in this population group [7-12]. Moreover, Iseki et al [12] found a strong association between low diastolic blood pressure and risk of death in a cohort of 1243 hemodialysis patients that were followed for 5 years and Zager et al [10] noted that the relative death rate for patients with pre- or postdialysis hypotension increased to four times normal or greater than 2.5 normal, respectively.

In a different approach, Klassen et al [13] investigated whether an increased pulse pressure would be associated with increased risk of death despite the inverse relationship between conventional blood pressure measures and mortality in patients with end-stage renal disease.According to their results after a follow-up period of 1-year, multivariable Cox proportional hazards modeling showed a direct and consistent relationship between increasing pulse pressure and increasing death risk. Each incremental elevation of 10 mm Hg in postdialysis pulse pressure was associated with a 12% increase in the hazard for death (hazard ratio, 1.12; 95% confidence interval, 1.06-1.18). Postdialysis systolic blood pressure was inversely related to mortality with a 13% decreased hazard for death for each incremental elevation of 10 mm Hg (hazard ratio, 0.87; 95% confidence interval, 0.84-0.90).

Blood pressure of hemodialysis patients varies with each hemodialysis session as a result of loss of excess fluid. In a recent publication, Moriya et al [14]tried to define clearly the time point at which the blood pressure is measured. For this purpose, home BP of patients was monitored twice a day for 1 wk (morning-after waking up and evening-before sleeping). During the same week, the BP was measured in the supine position before and after each dialysis session. The BP was measured with automated devices by the same method. The authors calculated the weekly averaged blood pressure (WABP) based on these 20 mBP measurements/week. According to their results, none of the components of pre- or postdialysis blood pressure was significantly different between patients with and without cardiovascular events. Pulse weekly averaged blood pressure, age, and human atrial natriuretic peptide were significantly higher in patients who died than in survivors. Kaplan-Meier method with a log-rank test demonstrated that survival free rate from cardiovascular events and that of all-cause mortality in patients with pulse weekly averaged blood pressure ≥70 mmHg were significantly lower than those in the remaining patients

The same authors have showed that the systolic and diastolic WAB are almost completely consistent with the wake-up BP on the next day after the middle dialysis session (R^2 =0.709, P<0.0001; R^2 =0.775, P<0.0001, respectively) suggesting that this measurement could be used instead of the WAB [15]. Agarwal *et al.* [16,17,18] reported the significance of self-recorded home BP three times a day during 1 week in HD patients and showed that home BP correspond to ambulatory BP and left ventricular hypertrophy in HD patients.

The above mentioned studies suggest that BP should rather be evaluated by the average of sequential monitoring during 1 wk and not by one-point measurement before or after dialysis or after waking up. Pulse pressure (PP) more accurately predicts adverse CVE than

systolic+/-diastolic BP; moreover since PP is a marker of arterial stiffness (the latter being markedly increased in dialysis patients) it is logical, from a pathophysiological point of view, to use pWAB as a target index for controlling BP and a useful prognostic marker of cardiovascular events or all-cause mortality of HD patients.

An interesting approach to the reverse epidemiology paradox in HD patients (including hypertension) has been suggested by Shoji et al, based on data collected from Japanese registries. Undoubtedly, the relative risk of death from CVD in HD patients is 10—30 as compared with the general population in Europe and the US [19]. A logical approach would assume that HD patients experience 10 to 30 times more CVD events than the general population. Nevertheless, the report of the registry data in Okinawa, Japan, suggests that this is not the case; the risk of occurrence of acute myocardial infarction was 2.5 times and 4.6 times higher in male and female HD patients, respectively, than the general population [20] while the risk of stroke was 5.7 times and 8.5 times higher in male and female HD patients in their sixties, respectively, than the general population of the same age category [21]. Although these data indicate that HD patients experience more CVE, they do not suffice to fully explain the 10-30 times higher risk of death observed in these patients. An intriguing explanation suggested by Shoji et al, lies in the relative risk of death after a given CVE (fatality). In fact, death rate in 30 days after acute myocardial infarction was 22.9% for the general population and 50.8% for hemodialysis patients in Okinawa, Japan [20]. The 50% survival period after acute myocardial infarction was 7.3 years for the general population, whereas it was one month for hemodialysis patients. Also, the death rate in 30 days after stroke was 12.3% for the general population and 46.6% for hemodialysis patients in Okinawa, Japan [21].

Another possible explanation for the association of low blood pressure with higher mortality rates in HD patients is the "reverse causation" phenomenon. Reverse causation suggests that it is not hypotension or normotension, per se, that is detrimental but rather the underlying condition causing low blood pressure (congestive heart failure or continuously erroneous estimation of dry weight); in other words, the reversion of the direction of the causal pathway that is responsible for this paradoxical association.

Nevertheless, even if the association of low blood pressure and mortality is somewhat a result of poor general health, strategies that would avoid hypotension (or even low normal blood pressure) in HD patients should be implemented.

3. Obesity and cholesterol levels in HD patients

Several epidemiologic studies have shown a strong relationship between obesity and increased risk of cardiovascular disease and mortality in the general population [22-23]. Nevertheless, several studies have indicated a J or U curve effect in individuals with a low BMI [23-25]. The first study to report that overall mortality risk decreased with increasing BMI was the Diaphane Collaborative Study Group in France. Participants were young, mostly nondiabetic, French patients treated with hemodialysis during the 1970s [26]. In the 1990s, Leavy et al [27] described the predictive value for mortality over 5 years of follow-up of a number of risk factors, recorded at baseline, in a national sample of 3607 hemodialysis patients. According to their results, low BMI was independently and significantly predictive of increased mortality; moreover its independent predictive value of mortality risk persisted even 5 years later. No evidence of increasing mortality risk was found for higher values of BMI. The prospective Dialysis Outcomes and Practice Study (DOPPS) [28,29] has allowed

comparison of BMI-mortality relationships in the United States and Europe and among a variety of "healthier," as compared with "sicker" hemodialysis patient subgroups, such as younger patients, never-smokers, and those with less chronic illnesses.

A BMI of 23 to 24.9 kg/m2, was associated with the highest relative mortality risk. Overall, a lower relative risk (RR) of mortality as compared with a BMI of 23 to 24.9 kg/m2, was found for overweight (BMI 25 to 29.9 kg/m2; RR 0.84; P = 0.008), for mild obesity (BMI 30 to 34.9 kg/m2; RR 0.73; P= 0.0003), and for moderate obesity (BMI 35 to 39.9 kg/m2; RR 0.76; P= 0.02). Even when patients were subdivided in different groups in respect to general health status, the results didn't change, contrary to the initial hypothesis of the investigators that reverse epidemiology may not exist in healthier or younger ESRD patients. There was a survival benefit for healthy overweight patients (BMI 25 to 29.9 kg/m2) that was even greater for the obese patients (BMI ≥30 kg/m2), and this was observed for the healthier as well as the sicker groups of hemodialysis-treated patients.

One could argue that although BMI is used as a general index to distinguish underweight, normal, overweight and obese patients, it doesn't provide information on the relative contribution of muscle and fat mass to overall body weight. This is of paramount importance since increased catabolism is common place in HD patients and this can lead to substantial decreases in muscle mass resulting in lower BMIs that could erroneously be interpreted as "normal". A recent study by Kalantar-Zadeh et al [30], investigated the relative contribution of fat versus muscle mass or their changes over time to the survival benefits of larger body size.

These investigators studied 121,762 patients receiving HD 3 times weekly from July 1, 2001, through June 30, 2006. They examined whether BMI (calculated using 3-month averaged post-HD dry weight) and 3-month averaged serum creatinine levels and their changes over time were predictive of mortality risk. They assessed muscle mass by using serum creatinine measurements since in long-term HD patients who have minimal or no residual renal function and who undergo a stable HD treatment regimen, time-averaged serum creatinine concentration is a more likely surrogate of muscle mass, and its changes over time may represent parallel changes in skeletal muscle mass[31,32]. According to their findings higher BMI (up to 45) and higher serum creatinine concentration were incrementally and independently associated with greater survival, even after extensive multivariate adjustment for available surrogates of nutritional status and inflammation. Dry weight loss or gain over time exhibited a graded association with higher rates of mortality or survival, respectively, as did changes in serum creatinine level over time. Among the 50,831 patients who survived the first 6 months and who had available data for changes in weight and creatinine level, those who lost weight but had an increased serum creatinine level had a greater survival rate than those who gained weight but had a decreased creatinine level. These associations appeared consistent across different demographic groups of patients receiving HD. These results suggest that in patients receiving long-term HD, larger body size with more muscle mass appears to be associated with a higher survival rate. A discordant muscle gain with weight loss over time may confer more survival benefit than weight gain while losing muscle. Moreover the combination of an increase in time averaged serum creatinine levels (a surrogate according to the authors of muscle mass) and total body weight is associated with higher survival rates than an isolated increase in muscle mass, suggesting that higher body fat content confers also a survival benefit in HD patients.

Several pathogenetic mechanisms have been proposed in order to explain the association of obesity with a higher survival rate in HD patients. A recent review by Kalantar-Zadeh et al has summarized these mechanisms (Table 1).

Potential pathophysiologic mechanisms concerning the Obesity paradox
Malnutrtion inflammation syndrome
Temporal delay between competitive risk factors: Increased nutrition vs malnutrition
Selection bias during progression of Chronic Kidney Disease
Sequestration of uremic toxins in fat tissue
Anti-inflammatory cytokines related to total body mass, adiponectines
TNF-α receptors
Endotoxin-lipoprotein hypothesis
Hemodynamic stability of obese patients
Neurohormonal alterations in obesity
Alteration of traditional risk factors in the uremic environment
Inverse causation
Survival bias
Advantages of obesity during human evolution

Table 1. Adapted from Kalantar-Zadeh [8,15,16].

4. Malnutrition inflammation syndrome

This hypothesis states that low BMI in HD patients is associated with increased inflammation meaning that underweight patients with ESRD would more likely become ill and would recover more slowly from illness compared with patients who have normal weight or who are obese. On the contrary, if overweight patients with an increase in adipose tissue develop a deficiency in energy or protein intake, they would be less likely to develop frank protein-energy malnutrition. This assumption, however, has not been adopted by other investigators of the obesity paradox. According to Beddhu et al, recent data suggest a cross-sectional association of high BMI or abdominal adiposity with inflammation both in persons with moderate chronic kidney disease (CKD) and in the dialysis population (33). Moreover in HD patients inflammation is associated with coronary artery calcification (34), myocardial injury as shown by elevations in serum troponin T (35), and death (36). These authors hypothesized that in HD patients, the effects of nutrition on survival are much stronger than are the effects of atherosclerotic events. Therefore, although undernourished patients have lower inflammation, they experience a higher rate of cardiovascular and noncardiovascular events than patients with normal or higher weight. On the other hand, better nutrition and adiposity, although associated with increased inflammation, oxidative stress and atherosclerotic changes is associated with better survival since it confers a survival advantage relatively to undernutrition.

5. Temporal delay between competitive risk factors: Increased nutrition vs malnutrition

It has been suggested that the obesity paradox is due to the presence of a temporal delay between competitive risk factors: a "fast killer" like the malnutrition-inflammation syndrome and a "slow killer" like obesity. It is noteworthy to bear in mind that 2/3 of dialysis patients die within the first 5 years of HD with this dramatic survival rate being worse than the 5-year survival in the majority of cancer patients. [37].

6. Selection bias during progression of Chronic Kidney Disease (CKD)

Chronic Kidney disease is associated with increased cardiovascular morbidity and mortality. In the United States almost 90% of the 20 million patients with CKD die before reaching dialysis due to cardiovascular events [38], meaning that only a small minority of these patients survive long enough to start dialysis. This observation suggests that there is a selection bias for survival, probably reflecting different genetic or metabolic profiles that determine which patients can overcome the increased risk of death in the pre-dialysis period and eventually start dialysis [39]. Arizona PIMA Indians are a typical example of this hypothesis; although they are obese and diabetic and develop CKD stage 5 rapidly, they are protected from cardiovascular disease probably because if high HDL-cholesterol levels [40]. Therefore, one can hypothesize that dialysis patients constitute a group of "survivors" that doesn't represent the totality of CKD patients and therefore the associations of high BMI and prolonged survival is erroneous in this group.

7. Sequestration of uremic toxins in fat tissue

This theory suggests that uremic toxins are sequestered in adipose tissue and therefore obese dialysis patients are "protected" more efficiently than lean dialysis patients from the deleterious effects of these toxins. A recent study has showed that a substantial reduction in body weight results in liberation in the circulation of lipophilic molecules (hexachlorobenzole, chlorated hydrocarbons) [41]. Weight loss is associated with a reduction in musculoskeletal oxidative metabolism, resulting in a decrease in anti-oxidant defensive mechanisms. [42]. The abovementioned events can possibly explain in part the in the relative risk of mortality in dialysis patients [43].

8. Anti-inflammatory cytokines related to total body mass, adiponectines and TNF-α receptors

Adipose tissue produces adiponectins and soluble receptors of TNF-α; these molecules antagonize the deleterious effects of inflammatory cytokines in the cardiovascular system resulting in an increase in cardiovascular protection. Moreover the soluble receptors of TNF-α neutralize the nocious biologic effects of this factor [44]. Leptin is mainly produced by adipocytes and metabolized in the kidney. Leptin is taken up into the central nervous system by a saturable transport system, and controls appetite. Leptin acts on peripheral tissue and increases the inflammatory response by stimulating the production of tumor necrosis factor alpha, interleukin-6 and interleukin-12. In healthy humans, serum leptin concentration is related to the size of adipose tissue mass in the body. The majority of obese subjects have inappropriately high levels of circulating plasma leptin concentrations, indicating leptin resistance. In healthy subjects increased leptin concentration constitutes a biomarker for increased cardiovascular risk. On the other hand, a recent prospective long-term study in patients with chronic kidney disease stage 5 on hemodialysis therapy showed that reduced serum leptin concentration is an independent risk factor for mortality in these patients. According to this study,a reduced serum leptin concentration is an independent risk factor for mortality in hemodialysis patients. During the follow-up period of almost 7 years the relative risk for mortality in 71 patients with chronic kidney disease stage 5 with serum leptin concentrations below the median (<2.6 lg/l) compared with patients above the median was 1.96 (45). These data indicate that higher serum leptin concentrations might be

advantageous in patients with chronic kidney disease stage 5. Other investigators showed that in patients with chronic kidney disease stage 5 leptin is not increased as a consequence of inflammation, but behaves as a negative rather than as a positive acute phase protein meaning that lower serum leptin concentrations are a marker of increased systemic inflammation.

9. Endotoxin-lipoprotein hypothesis

This hypothesis suggests that high levels of lipoproteins bind to and reduce the concentrations of circulatory endotoxines, resulting in an increased protection from their pro-inflammatory effects [46]. The same hypothesis has been suggested as an explanation to the paradox of increased survival of patients with chronic heart failure and high cholesterol levels [47].

10. Hemodynamic stability of obese patients

Obesity has been associated with higher blood pressure and therefore better endurance of ultrafiltration during HD and lower rates of hypotensive episodes [46].

11. Neurohormonal alterations in obesity

Sympathetic and renin-angiotensin system hyperactivity are associated with increased mortality both in heart failure and dialysis patients. It has been suggested that obesity diminishes the stress reponse and therefore "protects" the patient against the deleterious effects of increased acute neurohormonal activation [48].

12. Alteration of traditional risk factors in the uremic environment

Hypertension, dyslipidemia, tobacco smoking, diabetes mellitus and more recently obesity and hypertriglyceridemia are considered as the major risk factors for new cardiovascular morbidity and overall mortality in the general population. It is possible that the uremic environment and/or the water-sodium overload in HD patients can alter the function of the cardiovascular system; this scenario suggests that other non-traditional risk factors (i.e inflammation, disorders of divalent ion metabolism, secondary hyperparathyroidism, anemia, acidosis) are more important for overall survival [46].

13. Inverse causation

The association of low BMI with increased mortality may be only an epiphenomenon (in other words the result) and not the cause of the increased mortality observed in dialysis patients. This is a common source of bias in observational studies that focus only on the presence of an association without looking at the direction of causality [47].

14. Survival bias

Obesity is associated with an increase in cardiovascular morbidity and mortality in the long and not in the short term. This could be of particular importance in HD patients, since the latter don't live long enough to experience the nocious effects of obesity. It is worth noting

that almost 50% of HD patients die within 5 years after starting dialysis. Therefore, HD patients "benefice" of a high BMI for as long as they live since undernutrtion is the principal "fast killer" that is responsible for the inappropriately high mortality rate observed in this population group.

15. Conclusions

Albeit the fact that the reverse epidemiology paradox may be a misnomer, its use highlights a reality frequently observed in chronic disease states that has until recently been neglected: the relative impact of "classical" risk factors for cardiovascular morbidity and mortality is if not reversed at least significantly altered. This observation is stimulating for further research that eventually could unravel the mechanisms that underlie this phenomenon and deepen our knowledge concerning the altered physiology of chronic disease states, including dialysis. Perhaps, the best explanation of the reverse epidemiology paradox relies on the constantly altered physiology observed in chronic disease; it is this "reverse" physiology that is responsible for the reverse associations between classical risk factors and CVE.

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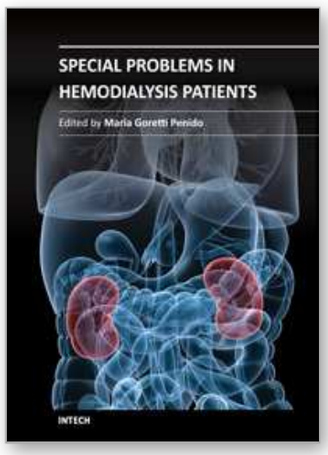
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Special Problems in Hemodialysis Patients

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This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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