

Phenomenon of reverse epidemiology in ESRD

Introduction

Many recent studies suggested that PEM and inflammation in dialysis patients are associated with decreased quality of life and increased hospitalization and mortality, especially from cardiovascular disease. Epidemiological studies indicated that hypoalbuminemia and increased serum CRP levels are strong predictor of poor clinical outcome in patients with ESRD (*Yeun JY; et al , 2000*).

Compared with such traditional risk factors as obesity, hypercholesterolemia, and hypertension, hypoalbuminemia per se, generally considered an indicator of MICS, has one of the most striking and consistent associations with clinical outcome in these individuals. (*Becker AE; et al , 2001*).

In highly industrialized affluent countries, PEM is an uncommon cause of poor outcome in the general population, whereas over nutrition is associated with a greater risk for cardiovascular disease and has an immense epidemiological impact on the burden of this disease and shortened survival. Conversely, in maintenance dialysis patients, undernutrition is one of the most common risk factors for adverse cardiovascular events (*Kalantar-Zadeh K; et al, 2003*).

Hence, certain markers that predict a low likelihood of cardiovascular events and improved survival in the general population, such as decreased BMI (*Port FK; et al, 2002*) or lower serum cholesterol levels, (*Iseki K; et al, 2002*) are risk factors for increased cardiovascular morbidity and death

in dialysis patients. (*Kalantar-Zadeh K; et al, 2003*) Paradoxically, obesity, hypercholesterolemia, and hypertension appear to be protective features associated with greater survival among dialysis patients. A similar protective role has been described for high serum creatinine and possibly homocysteine levels in patients with ESRD. The association between undernutrition and adverse cardiovascular outcome in dialysis patients, in contrast to that in individuals without ESRD, has been referred to as reverse epidemiology. and hence comes the importance of studying this phenomenon and its impact in ESRD patients (*Kalantar-Zadeh K; et al, 2003*).

I. HISTORY OF REVERSE EPIDEMIOLOGY:

The term “reverse epidemiology” was first mentioned by some epidemiologists in the Center for Disease Control and Prevention and the National Cancer Institute (NCI) in late 1990`s in conjunction with the novel near real-time DNA fingerprinting to identify clinical isolates of food-borne pathogenic bacteria or cancer cells. (*Swaminathan B, 2003*).

This new methodology, by enabling early recognition of food-borne disease clusters as the source of outbreaks, appears to circumvent the traditional outbreak investigations that are usually initiated by epidemiologic methods as the first step to be followed by focused biochemical investigations. The “reverse epidemiology” indicates the reversal of epidemiology-biochemistry hierarchy in contrast to the traditional outbreak investigations. Similarly, the NCI cancer epidemiologists used the term “reverse epidemiology” in the context of the ability to look at genetic changes in cancer cells to the search for external causes of cancer, again

circumventing the traditional need to conduct a priori epidemiologic analyses. (*Klausner, M.D, 1997*).

It appears that the term “reverse epidemiology” was first introduced to the nephrology arena by *Coresh* during his lecture at the 1999 American Society of Nephrology annual conference in Miami, FL. (*Levin NW; et al, 2007*). Subsequently, Kalantar-Zadeh et al. repeated this terminology in several publications including a Perspective in Renal Medicine article in *Kidney International* in March 2003, (*Kalantar-Zadeh K; et al, 2003*) in that the concept of reverse epidemiology was systematically described in dialysis patients. Kalantar-Zadeh et al. also introduced this concept in a cardiology journal to describe the similar counterintuitive associations in heart failure patients. (*Kalantar-Zadeh K; et al, 2004*).

Since then the notion of reverse epidemiology has found to be even more inclusive, as it has gone beyond the dialysis and heart failure patients and now relate to a number of different populations with chronic disease states and wasting syndrome including geriatric populations. It is estimated that almost 30 million Americans with chronic disease states or advanced age exhibit a reverse epidemiology. (*Kalantar-Zadeh K; et al, 2007*)

Hence, in approximately 10% of the US population, the Framingham paradigm based recommended target ranges for BMI, lipid or blood pressure may not apply and may even cause more harm than help. Any new scientific concept should have an appropriate terminology to be optimally represented. The term “reverse epidemiology” has been criticized with the argument that the science of epidemiology cannot be reversed. (*Foley RN, 2004*). This reasoning is indeed surprising, because it must be clear to such astute critics

that the term does not pertain to the entire field of epidemiology. This is not the first time that the word “reverse” is used in association with the name of an entire discipline to indicate a focused concept. There are indeed such similar terminologies as:

- reverse genetics (*Tronche F; et al , 2002*)
- reverse pharmacology (*Sakurai T, 2005*)
- reverse physiology (*Birgul N; et al , 1999*)
- reverse cardiology (*Plutzky J, 2003*)
- reverse endocrinology (*Kliwer SA; et al , 1999*)
- reverse immunology (*Viatte S; et al , 2006*)

Each of these designations has very specific focus and does not imply that the field of genetics, pharmacology, physiology, cardiology, endocrinology or immunology is reversed. The critics are encouraged to focus on the flaws of the concept of reverse epidemiology rather than being obsessed with the terminology.

In the past 5 years, the term reverse epidemiology has been established as a recognized scientific term and used by many authors (*Kopple JD, 2005*).

The term has been incorporated by the “National Library of Medicine” as a valid search term. And at (June 2007) PubMed has listed over 40 articles that include the term “reverse epidemiology” in their titles or abstracts.

In Google search, there are over 300 websites on reverse epidemiology and over 13,000 websites that are cross referred to reverse epidemiology. In February 2006, the concept of reverse epidemiology was found to be the leading “emerging research front” in the entire field of clinical medicine.

(*Thomson Scientific Solutions, 2006*). This exponential growth and recognition can only indicate that there must be some degree of scientific appeal with both the term and the concept of reverse epidemiology

II. clinical outcome and reverse epidemiology

As well known, high blood pressure (BP), obesity and hypercholesterolaemia are established risk factors for the development of cardiovascular diseases (CVD) and cerebrovascular events (**Kenchaiah SE; et al, 2002**).

Chronic Renal Failure (CRF) has been recognised as an independent risk factor as well (**Sarnak MJ; et al, 2003**). In this respect, it has been speculated that the accumulation of uraemic toxins with a molecular weight of 1-50 kilo Dalton plays an important role. In addition, in hemodialysis patients, haemodialysis treatment itself might contribute to the development of CVD (**Nubé MJ, Vervloet MG, 2000**).

During haemodialysis the coagulation cascade and the complement system are activated, whereas several blood cell elements are stimulated. As a result, leucocytes and platelets release intracellular granule products, such as myeloperoxidase and platelet factor 4, respectively. Furthermore, during haemodialysis an increase in the serum concentrations of endothelial-derived surface molecules has been described, suggesting endothelial activation. Despite important modifications in the dialysis equipment in the last three decades, the overall mortality of chronic haemodialysis (CHD) patients remains unacceptably high. In fact, mortality in these patients is 10 to 20 fold compared with the general population and even worse in the younger

age groups. Of interest, left ventricular hypertrophy (LVH) is found in 70% of the patients starting haemodialysis.

It used to be thought that CVD resulted from a combination of traditional, uraemic and haemodialysis-related risk factors in patients with end-stage renal disease (ESRD). This concept has been challenged recently, as both BP and serum cholesterol values are often within the normal range in CHD patients (*Iseki KI; et al, 2002*).

In fact, whereas traditional risk factors for CVD are correlated with an unfavourable outcome in the general population, in CHD patients these factors appear to be protective and associated with an improved survival. In recent years, several studies have been published on this phenomenon of unexpected, paradoxical observations in CHD patients, which is referred to as 'reverse epidemiology'.

III. Elements of Reverse Epidemiology

An example of risk factor reversal is the relation between body weight and the hazard ratio (HR) of mortality. In the general population, the mortality rate decreases as the body weight for height or the body mass index (BMI) is reduced (*Port FK; et al, 2002*). A "J" or "U" curve relation has been described in some studies of normal persons, whereby mortality rates begin to rise as the BMI (in kg/m²) drops below about 19–22 (*Port FK; et al, 2002*).

In other studies of normal persons, the mortality rate continues to fall as the BMI decreases to about 19 or lower. If the effects of cigarette smoking, the lifestyle of many cigarette smokers, and the weight-lowering effects of illnesses, including subclinical diseases, are excluded, leanness as a risk

factor for mortality often disappears. In maintenance hemodialysis (MHD) patients, in contrast to the above observations, the relation between body weight–for height or BMI and mortality represents the reverse, and often the mirror image, of the normal association (*Port FK; et al , 2002*).

This reversed relation has been reported in virtually all epidemiologic studies in MHD patients of the relation between body weight–for-height and mortality, although some exceptions to this general rule are found, particularly in Asian patients.

The inverse relation between weight-for-height and mortality was observed in studies from both the United States and Europe, and it is particularly strong when the comparison is limited to MHD patients whose body weight–for-height ranges from approximately normal to low values. (*Wong JS; et al, 1999*).

However, the trend toward greater survival with increasing weight for height or BMI in MHD patients continues into the obese range, perhaps particularly for unadjusted comparisons. A continued decrease in the risk factor ratio for mortality has even been observed in MHD patients with BMIs >45. The direct relation between obesity and survival in MHD patients persists over such a large range of body weights that unadjusted survival rates are greater in MHD patients with a BMI >45 than in those with a BMI 25–27.5. A reversal of the normal weight-for-height versus mortality relation has also been observed among chronic peritoneal dialysis (CPD) patients. (*Chung SH; et al, 2000*).

In these various studies, the serum total cholesterol concentration associated with the lowest HR of death in MHD or CPD patients is about

160–200 mg/dL. This stands in contrast to the relation of low serum cholesterol to improved survival that exists in the general population.

Only one study in maintenance dialysis patients reported an association between elevated serum cholesterol and increased mortality, and that study was conducted in 190 CPD patients with a mean follow-up of 12 months. Recently Kalantar et al (2004) found that low serum LDL-cholesterol concentrations also were associated with an increased HR of death in MHD patients. On the other hand, increased serum lipoprotein(a) is associated with decreased survival in maintenance dialysis patients, as it is in the general population. The relation between systolic blood pressure and the HR of death is also abnormal in MHD patients. In the general population, the data clearly indicate that hypertension is associated with an increased risk of adverse cardiovascular and cerebrovascular events and mortality due to those events (*Van Den Hoogen PCW; et al, 2000*).

Several surveys in large populations of MHD patients either did not find high blood pressure to be an independent risk factor for cardiovascular disease CVD or for mortality or found lower blood pressures not to be protective of mortality. Some studies found that systolic and diastolic hypertension posed little or no increased risk for CVD or for mortality or that it actually lowered the risk for these adverse events. (*Cheung AK; et al, 2000*).

These relations were examined with blood pressures obtained immediately before a hemodialysis treatment (i.e., when patients' total body sodium, chloride, and water are increased, which tends to engender higher blood pressures) or after a hemodialysis session (i.e., when patients have had

excess sodium, chloride, and water removed, which tend to promote lower blood pressures). The systolic blood pressures associated with the lowest HR of death were about 120–180mmHg before dialysis and 120–169mm Hg after dialysis (*Fleischmann EH; et al, 2001*).

Elevated plasma total homocysteine (tHcy) concentrations are associated with an increased relative risk of death in the general population. This is consistent with a large body of experimental evidence indicating that homocysteine is toxic to vascular endothelium, promotes atherosclerosis, and predisposes to arterial thrombosis (*Hoffman MA; et al, 2001*).

Several studies in CRF patients not on dialysis or in maintenance dialysis patients show a similar relation between higher plasma tHcy and the risk of CVD (*Mallamaci F; et al, 2002*). On the other hand, Bostrom et al (1996) found no relation between plasma homocysteine and the prevalence of CVD in maintenance dialysis patients, and several studies showed a reverse relation between plasma tHcy concentrations and the risk of CVD or cardiovascular mortality (*Bostrom; et al, 1996*). Kalantar et al (2003) found that MHD patients who were in the higher quartiles of homocysteine concentrations tended to have the lowest morbidity and mortality, whereas those in the lowest quartile of serum homocysteine concentrations clearly had the highest relative risk of morbidity and mortality, including cardiovascular death (*Kalantar-Zadeh K; et al, 2004*).

This inverse relation between plasma homocysteine and relative risk of death persisted even after multivariate adjustment for other risk factors associated with CVD such as age, diabetes mellitus, sex, race, ethnicity, and serum albumin concentrations. It is noteworthy that plasma tHcy is elevated

in about 85–95% of MHD patients, usually to about 1.5–2.5 times the upper limit of normal serum concentrations. Because almost all maintenance dialysis patients have high plasma tHcy, and because these persons may also be at increased risk for CVD, the reverse risk factor findings regarding homocysteine in maintenance dialysis patients are, strictly speaking, not necessarily in conflict with the findings in the general population. (*Kalantar-Zadeh K; et al, 2004*).

Similar reverse epidemiologic observations have been made for serum creatinine and parathyroid hormone (PTH). These studies show that, in MHD patients, the relation between the measure and outcome is counterintuitive. Thus, serum concentrations of creatinine, a metabolic product that increases in serum as renal function falls and that has been reported in some in vitro studies to have toxic effects (*Kopple JD., 2001*) , are often 8–15 times normal in both MHD and CPD patients. People with a modest rise in serum creatinine (ie, with mild to moderate renal insufficiency) are at increased risk of morbidity and mortality, including adverse cardiovascular events (*Go AS; et al, 2004*).

In contrast, in MHD patients, serum creatinine concentrations in blood obtained before the onset of a hemodialysis treatment or in the morning (for peritoneal dialysis patients) are inversely associated with the relative risk of mortality (*Kalantar-Zadeh K; et al, 2001*).

An elevated serum PTH concentration, which is a common phenomenon in nondialyzed CRF and maintenance dialysis patients, is considered to be a uremic toxin that may have pervasive adverse effects (*Massry SG, 2001*).

Hyperphosphatemia occurs frequently in renal failure and is a cause of hyperparathyroidism. Increased serum phosphorus is reported to be a risk factor for higher morbidity and mortality in MHD patients. However, 2 epidemiologic studies in MHD and CPD patients show that those persons whose serum PTH concentrations are less elevated (but still may be greater than normal) have higher mortality rates (*Guh JY; et al, 2002*).

In summary elements of reverse epidemiology are:

- .Body mass index (*Nishizawa Y; et al, 2003*).
- .Total cholesterol level (*Leavey SF; et al, 2001*).
- .Low density lipoproteins (*VanDenHoogenPCW; et al, 200*).
- .Hypertension either systolic or diastolic (*Klassen PS; et al, 2002*).
- .Serum homocysteine (*Kalantar-Zadeh K; et al, 2001*).
- .Serum creatinine level (*Kala tar-Zadeh K; et al, 2001*).
- .Serum parathyroid hormone (*Kalantar-Zadeh K; et al, 2001*).

IV. POSSIBLE CAUSES OF PARADOXICAL RISK FACTORS

In patient with maintenance dialysis, important independent predictors of mortality and morbidity are CRP (marker of inflammation), pre-albumin (marker of nutrition), so it is strongly thought that malnutrition and inflammation have some relation to do with this reverse epidemiology (*Mehrotra R and Kopple JD, 2004*). Malnutrition in CRF is common complication that occurs in relatively high percentage of patient, many factors share in this problem including low nutrient intake, nutrient loss during dialysis, hypercatabolism due to coexistent acute or chronic illness and others (*Mehrotra R and Kopple JD, 2004*).(*vide supra*)

Also patients with CRF frequently show evidence of inflammation including elevated CRP, serum amyloid A and decrease level of serum albumin, transferrin, cholesterol carrying lipoprotein and prealbumin (*Stenvinkel P and Yeun JY ,2004*).(*vide supra*).Many factors are responsible for chronic inflammation process including comorbid illness, CRF itself which increase numbers of pro- inflammatory cytokines, reaction to vascular access or to hemodialyser itself and others (*Hoffman MA; et al ,2001*) Despite important modification in dialysis therapy the overall mortality of dialysis patient remains unacceptably high that may increase up to 10 or 20 fold compared to general population (*Exerpts from the U.S, R.D.S 2005*), Hence comes the importance of paradoxical risk factors which can change our goal of some of the main measures used to clinically assess dialysis patients.

Body mass index and reverse epidemiology

Introduction

As well known obesity is an established independent risk factor of CVD in the general population. it was shown in a Dutch study of 8100 females who were followed for 17 years that both total and cardiovascular Mortality was greatest in the highest body mass index (BMI) quartile ($>27.7 \text{ kg/m}^2$) (*Maru S; et al , 2004*).

In 1982 Degoulet et al. reported for the first time that underweight was associated with an increased mortality in CHD patients (*Degoulet P; et al , 1982*).

Conversely, in a historical prospective study on 1346 CHD patients, BMI more than 27.5 kg/m² was correlated with the highest survival, if compared with low (less than 20 kg/m²) and normal (20 to 27.5 kg/m²) BMI values (*Fleischman E; et al , 1999*).

After correction for various influencing factors, such as race and serum albumin, BMI appeared to be an independent positive predictor of survival in CHD patients. Comparable results have been obtained in several observational studies. In a large retrospective analysis of 10,000 CHD patients the RR for mortality was 0.84 in overweight patients and 0.78 in individuals with obesity (*Leavy SF; et al , 2001*).

Few studies, usually based on a small sample size, have shown a deleterious effect of high BMI in CHD patients. For instance, Kaizu et al (1998). Studied 116 Japanese CHD patients who were followed for 12 years and found BMI >23 kg/m² correlated with a lower survival rate than BMI 17.0 to 18.9 kg/m². Based on these data it was speculated that high BMI is advantageous in the short term, but not over a longer period of time.

Table 5. Summary of key references related to obesity and survival on dialysis

| References | Dialysis type | Patient details | Body mass measures | Effect of body mass on survival |
|--------------------------|--------------------------|---|--------------------------------|--|
| Degoulet et al., 1982 | Hemodialysis (HD) | 1453 subjects treated in 33 French dialysis centers; 5-year observation | Body Mass Index (BMI) | Greater mortality with lower BMI; no increased mortality with higher BMI |
| Leavey et al., 1998 | HD | Data on 3607 subjects from US Renal Data System (USRDS), 5-year observation | BMI | Greater mortality with lower BMI; no increase in mortality with higher BMI |
| Kaizu et al., 1998 | HD | 116 Japanese hemodialysis patients, 5-year observation | BMI | Greater mortality with lower and higher (BMI > 0.19) BMI |
| Fleischmann et al., 1999 | HD | 1346 patients (Renal Care Group, MS cohort), mostly African Americans, 1-year prospective follow-up | BMI | BMI Greater mortality with lower BMI, but lower mortality, fewer hospital admissions, and shorter stay with greater BM; better nutrition with higher BMI |
| Kopple et al., 1999 | HD | 12,965 patients, 1-year observation | Body weight, weight for height | Lower mortality with progressively higher weight for height; lowest mortality rates in overweight patients |
| Wong et al., 1999 | HD | 84,192 Asian Americans and whites from USRDS; 2-year observation | BMI | Lower mortality in Asian Americans than whites; higher mortality with overweight and obesity BMI |
| Wolfe et al., 2000 | HD | 9165 USRDS patients; 2-year prospective observation | Body weight, body volume, BMI | Close association with body measures and dialysis survival even in overweight and obese patients |
| Johnson et al., 2000 | Peritoneal dialysis (PD) | 43 patients; 3-year follow-up | BMI | Better survival in overweight PD patients |
| Leavey et al., 2001 | HD | 9,714 U.S. and Europe (DOPPS) patients, variable follow-up | BMI | Mortality risk decreased with increasing BMI, even in obese patients |

continued

| | | | | |
|-----------------------------|-------|--|--|---|
| Combe et al., 2001 | HD | 1,610 patients in 20 French centers; 2.5-year observation | BMI | No positive influence of BMI on survival; average BMI, 23 |
| Port et al., 2002 | HD | Data on 45,967 patients from HCFA billing records | BMI | The highest BMI tertile had the lowest mortality risk |
| Lowrie et al., 2002 | HD | 43,334 patients; Fresenius Medical Care (North America) clinical data system | Body weight, weight/height, BSA, and BMI | Better survival with large body mass |
| Aslam et al., 2002 | PD | 104 patients; 2-year observation | BMI | No survival difference between normal and overweight patients |
| Johanson et al., 2004 | HD/PD | 418,055 patients; USRDS data patients beginning dialysis over a 5-year period; average follow-up 2 years | BMI, Benn index, and estimated fat mass | Lower mortality and hospitalization in obese; relationship seen in all ethnicities except Asians |
| Kalanteh-Zadeh et al., 2005 | HD | 54,535 maintenance patients from virtually all DaVita dialysis clinics in the United States | BMI | Lower all-cause and cardiovascular mortality for higher BMI using different cutoff up to 35; weight loss associated with increased mortality |
| Beddhu et al., 2005 | HD | In 70,028 patients who initiated hemodialysis in the United States from January 1995 to December 1999 with measured creatinine | BMI; 24-hour urinary creatinine (estimate of LBM) | Normal BMI and higher urinary creatinine reference; high BMI, higher urinary creatinine had lower mortality; patients with low urinary creatinine had worse outcomes whether their BMI was high and low |
| Kakiya et al., 2006 | HD | Observational cohort study in 808 Japanese patients with ESRD mean follow-up, 53 months | BMI, fat mass index by DEXA; lean mass (BMI-FMI) | Higher FMI was associated lower mortality; higher LMI was not |
| Kalanteh-Zadeh et al., 2006 | HD | 535 adults; longitudinal, prospective study; 30 months | Body fat measure with infrared interactance; midarm muscle circumference; serum creatinine | Low % body fat associated with higher mortality; no survival advantage for the highest body fat > 36%; higher body fat associated with lower selfreported quality of life |

Quoted from Darren S. Schmidt and Abdulla K. Salahudeen, 2007).

Imprecision of the BMI to Evaluate Obesity

The BMI has become the tool for defining obesity, particularly in epidemiologic studies. It is easy to calculate and has no inherent cost. However, the BMI is not without its limitations:

1. It does not account for the relative contribution of fat to body size; so while obesity implies an excess of adiposity, someone with excess lean body mass will have an elevated BMI as well (*Beddhu S; et al , 2003*).
2. Also, variations in bone density can affect BMI; African Americans are known to have higher bone density than white subjects, whereas Asians on the whole have lower bone density.
3. Furthermore, while desired weight may vary with ethnicity, sex, and age, the typical cutoffs used to define normal, overweight, and obese make no allowances for these variations.

Although most of the studies that followed the initial reports of the obesity-survival paradox have continued to use the BMI to define body size and obesity, some studies have employed other means. Serum and urine creatinine levels have been used to make inferences about lean body mass (*Kalantar-Zadeh K; et al, 2005*). Others have used infrared interactance and dual x-ray absorptiometry (DEXA) scans to estimate different aspects of body composition (*Kakiya R; et al , 2006*).

In studying a USRDS cohort of 70,028 dialysis patients with ESRD, in whom dialysis was initiated between 1995 and 1999, they examined the effect of body size on mortality. In addition, they used timed urinary creatinine excretion in these ESRD patients as a surrogate marker for lean body mass. Patients with a BMI > 25 at baseline had a lower hazard ratio

(HR) for death (0.85, $p < 0.001$) than did those with a BMI of 18.5–24.9 (*Beddhu S; et al , 2003*).

Subjects who had low urine creatinine excretion (less than 0.55 g /day of creatinine in their urine, representing the lowest 25th percentile) had worse survival than those with urine creatinine excretion in the highest 75th percentile. Subjects were divided into “low” lean body mass and “normal” lean body mass based on a urinary creatinine cutoff at the 25th percentile ; a likely presumption here is that urinary creatinine excretion is proportional to lean body mass in these new dialysis patients. Those subjects with normal BMI and normal lean body mass, presumed to represent patients with relatively low fat mass, were designated as the control group. Those subjects with high BMI and normal lean body mass, presumed to have more fat mass, had a decrease in HR for death 0.85, 95% confidence interval (CI), 0.83–0.87 (*Beddhu S; et al , 2003*).

Those individuals with high BMI and low lean body mass (presumed highest body fat) did worse than the controls, as did those with normal BMI and low lean body mass. The authors of that report concluded from this that “the protective effect conferred by high BMI is limited to patients with normal or high muscle mass.” An alternative conclusion can be drawn from their study: BMI and lean body mass both have protective value, and the independent association implies a benefit from fat mass as well (*Schmidt D and Salahudeen A., 2007*).

Body Size, Body Composition and Outcomes in Dialysis Patients

Leavey et al. (1998) found that, in contrast to that reported for healthy adults, a high BMI has reduced mortality risk in hemodialysis patients. Similar results have also been reported by other studies consistently (**Johansen KL; et al , 2004**) .

This inverse association of BMI with mortality has been suggested as a risk factor paradox or reverse epidemiology for cardiovascular disease in uremic patients (**Kalantar-Zadeh K; et al , 2003**) and raises the question whether obesity confers a survival advantage in dialysis patient.

However, high BMI might result from high muscle mass, fat mass or both. High BMI because of high muscle mass might be more protective than high BMI because of high fat mass. In a study of incident hemodialysis patients in the United States from January 1996 to December 1998 with reported measured creatinine clearances at initiation of dialysis, BMI was used in conjunction with 24-hour urinary creatinine excretion (an indicator of muscle mass) to estimate body composition and examined the effects of estimated body composition on all-cause and cardiovascular mortality . (**Beddhu S; et al , 2003**).

Large body size was associated with better survival. However, compared to normal BMI, normal or high muscle patients, those with high BMI and low muscle mass (inferred high fat mass) had increased mortality whereas those with high BMI and normal or high muscle mass (inferred low fat mass) had decreased mortality. These data suggest that high BMI is not uniformly associated with better survival and the body composition is important in high BMI dialysis patients. In another study of incident

peritoneal dialysis patients, similar results were found (*Ramkumar N; et al , 2005*).

Body Size, Body Composition and Cardiovascular Risk Factors in Cardiovascular Disease in Dialysis Patients

Although high BMI is associated with better survival in dialysis patients, the associations of adiposity with traditional cardiovascular risk factors, such as diabetes and nontraditional risk factors, such as inflammation are not confined to the non dialysis population. Indeed, previous studies have shown that in dialysis patients, adiposity and or high BMI is associated with insulin resistance , diabetes , inflammation , anemia , coronary calcification and carotid atherosclerosis (*Yamauchi T; et al , 2003*).

It is perplexing that, if adiposity is associated with these apparent cardiovascular risk factors, why adiposity is associated with better survival in dialysis patients.

However the most plausible one explain that this dual effect of obesity can occur if:

1. Adiposity has dual competing effects on survival; a protective nutritional effect and a deleterious metabolic effect resulting in insulin resistance, dyslipidemia, hypertension and inflammation
2. The level of kidney function modifies the relative importance of these effects.

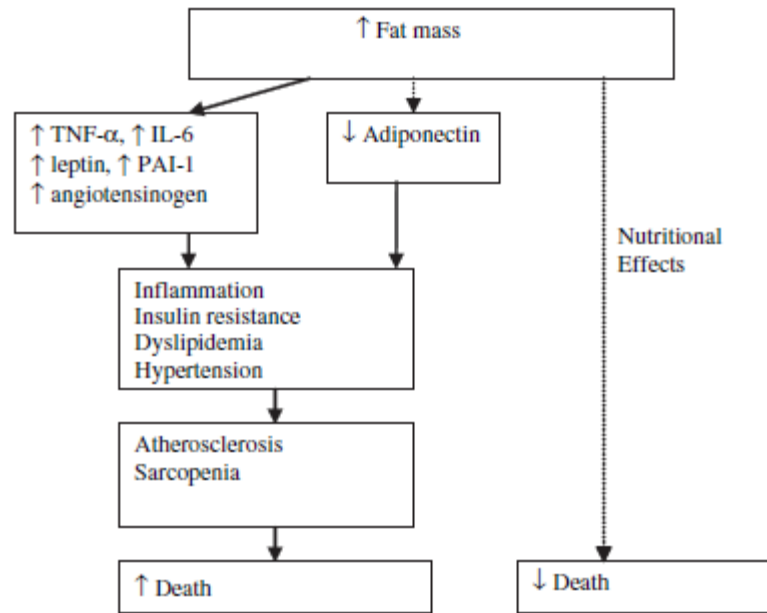


Figure 4. Hypothesized competing dual effects of fat mass on survival in CKD.
Quoted from Bonnie C. H. Kwan and Srinivasan Beddhu. 2007).

Meaning the deleterious metabolic effects of obesity outweigh its protective nutritional effects in the non-CKD population, the deleterious metabolic effects of obesity are neutralized by its protective nutritional effects in the moderate CKD population and the deleterious metabolic effects of obesity are outweighed by its protective nutritional effects in stage (V) CKD on dialysis.

The over-all effects of obesity on survival vary according to the level of kidney function and there is an interaction of body size and presence or absence of CKD on survival. Thus, despite an association of adiposity with better survival, it could still be associated with increased traditional and nontraditional cardiovascular risk factors and disease in dialysis patients. *(Bonnie C. H. Kwan and Srinivasan Beddhu. 2007).*

Also it is to be noticed that obese patients represent a more stable hemodynamic status, as many dialysis patients have some degree of heart failure or are in some relative state of fluid overload. Despite having similar pulmonary capillary wedge pressure and cardiac indices, overweight and obese patients with heart failure tend to have higher systemic blood pressure values. Hence, there appears to be an improved hemodynamic tolerance to after load-reducing agents. This may explain why a larger proportion of obese and overweight patients take angiotensin-converting enzyme inhibitors, which are known to prolong the lives of patients with advanced heart failure and that may also confer survival advantages to maintenance dialysis patients (*Horwich TB; et al , 2001*) .

Obesity and uremia

- White adipose tissue can be considered as the largest secretory organ in the body. Adipocytes produce a wide range of protein signals and factors termed adipokines . These include tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), plasminogen activator inhibitor (PAI-1), leptin, angiotensinogen, monocyte chemotactic protein-1, macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor and adiponectin. They serve as the signals for the effects of adipocytes on insulin resistance, inflammation, dyslipidemia, hypertension, and atherosclerosis (*Trayhurn P, Wood IS., 2005*).

Clinical effect of adipokines in uremic patients:

There is evidence that clinical effects of adipokines in dialysis patients parallel those observed in the nondialysis population.

- **Insulin Resistance** :there is a paucity of information in the CKD population on the associations of TNF- α and IL-6 with insulin resistance, plasma insulin levels and homeostatic model assessment (HOMA) index, a measure of insulin resistance, were negatively associated with plasma adiponectin concentrations in moderate CKD and dialysis patients. Further, increase in visceral fat mass or BMI is associated with insulin resistance and diabetes. Thus, it is plausible that adipokines mediate insulin resistance in dialysis patients (*Becker B; et al, 2005*).

- **Inflammation:** Pro-inflammatory adipokines, such as IL-6 and TNF- α stimulate the production of C-reactive protein (CRP) in the liver (*Whitehead JP; et al , 2006*). In CKD population, adiposity is associated with inflammation . In dialysis patients, plasma IL-6 had significant positive correlation with plasma high sensitivity C-reactive protein (hsCRP) in a cross-sectional analysis. Furthermore, plasma CRP concentrations inversely correlate with adiponectin in the general population (*Guebre-Egziabher F; et al , 2005*).

- **Dyslipidemia** Adiposity is associated with hypertriglyceridemia and low plasma high-density lipoprotein (HDL)-cholesterol concentrations in the general population. TNF- α is considered to play a role in hypertriglyceridemia by inhibiting lipoprotein lipase. Hypoadiponectinemia is associated with decreased plasma lipoprotein lipase activity, thereby promoting dyslipidemia. In dialysis patients, plasma adiponectin levels were inversely associated with plasma triglyceride concentrations ($r =$) 0.41 in men and 0.39 in women) and directly associated with HDL-cholesterol concentrations

($r = 0.28$ in men and 0.26 in women) in cross-sectional analyses (*Zoccali C; et al , 2002*).

- **Hypertension** In the general population, adipokines may play a causative role in hypertension by decreasing availability of nitrous oxide, a potent vasodilator and increasing endothelin, a potent vasoconstrictor. However, a small cross-sectional study suggested that plasma nitrous oxide levels were lower and endothelin levels higher in hypertensive hemodialysis patients compared to normotensive dialysis patients (*Erkan E; et al , 2002*).

- **Atherosclerosis** Increased plasma adiponectin concentrations were associated with lower hazard of cardiovascular events in CKD patients not on dialysis and in hemodialysis patients. On the other hand, elevated IL-6 concentrations are associated with progressive atherosclerosis in dialysis patients. Thus, adiposity and adipokines might be associated with atherosclerosis in the dialysis patients as in the general population (*Stenvinkel P; et al , 2002*).

From all these data it seems that Fat mass might have dual competing effects on survival in dialysis patients; a protective effect mediated through nutrition and a deleterious effect mediated through adipokines. Hence, increase in fat mass in dialysis patients is still associated with inflammation, insulin resistance, atherosclerosis and coronary calcification despite a protective effect of fat mass on survival. Thus, strategies that decrease the deleterious effects of fat mass without diminishing nutritional effects in dialysis patients could result in improved survival of these patients. As adipokines likely mediate the negative effects of fat mass, it is important to understand the effects of uremia on adipokine production, and examine the

role of adipokines on survival in hemodialysis patients. (*Zoccali C; et al , 2002*).

Table 6. Adipokines and atherogenesis

| Adipokine | Effect on vascular endothelium and atherogenesis |
|-----------------|--|
| TNF- α | ↓ NO bioavailability, ↓ Vasodilation ↑ NF κ B, ↑ VCAM-1, ICAM-1, E-selectin and MCP-1 |
| IL-6 | ↑ ICAM-1, E-selectin, VCAM-1 and MCP-1 ↑ Smooth muscle cell proliferation and migration |
| Leptin | ↑ Endothelin-1, ↑ reactive oxygen species and oxidative stress |
| Angiotensinogen | ↓ NO bioavailability ↑ NF κ B, ↑ VCAM-1, ICAM-1, PAI-1 |
| PAI-1 | ↑ Thrombus formation |
| Resistin | ↑ ET-1 release, ↑ VCAM-1, ICAM-1 |
| Adiponectin | ↓ NF κ B, ↓ VCAM-1, ↓ ICAM-1 and ↓ E-selectin ↓ Transformation of macrophages to foam cells ↓ Vascular smooth muscle cell proliferation and migration |

NO, nitrous oxide; NF κ B, nuclear transcription factor kappa B; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1

Quoted from Bonnie C. H. Kwan and Srinivasan Beddhu.2007.

Review of Studies that Have Assessed the Association between BMI and Survival in PD Patients

Table 7 .Summary of key references related to BMI and Survival in PD

| Author | Study design (number of subjects) | Outcome of interest |
|-----------------|---|--|
| Abbott et al. | Retrospective cohort analysis of USRDS Wave II DMMS-II ($n = 3337$) | 5-year patient survival on PD, BMI ≥ 30 vs. < 30 |
| Aslam N, et al. | Case-control ($n = 208$) | 2-year patient survival on PD, BMI > 27 vs. BMI 20–27 |
| Johnson et al. | Prospective, observational ($n = 43$) | 3-year patient survival on PD, BMI > 27.5 vs. BMI 20–27.5 |
| McDonald et al. | Retrospective cohort analysis of ANZDATA registry ($n = 9679$) | Up to 10-year survival of PD patients, BMI ≥ 30 vs. BMI 20–24 |
| Snyder et al. | Retrospective cohort analysis of USRDS ($n = 418,021$) | 3-year survival of PD patients, BMI > 29.9 vs. BMI 18.5–24.9) |
| Stack et al. | Retrospective cohort analysis of USRDS ($n = 134,728$) | 2-year survival of PD patients by BMI quartile |

(Quoted from Kevin C et al, 2007)

Reverse Epidemiology of Hypertension in the ESRD

Introduction

Eighty percent of a 250 000 maintenance hemodialysis (MHD) patients in the United States have systolic hypertension (HTN) (*United States Renal Data System, 2003*). Approximately two thirds of American MHD patients

die within 5 years of initiation of chronic dialysis treatment, mostly because of cardiovascular (CV) disease. HTN is a known risk factor of CV disease in the general population. hence, and HTN has been implicated as a major cause of poor clinical outcome and high mortality in MHD patients. However, efforts to treat conventional CV risk factors in MHD patients including HTN, hypercholesterolemia, and hyperhomocysteinemia have not resulted in significant improvement of their poor clinical outcome (**Vasan RS et al, 2001**)

Surprisingly, several recent studies have indicated an inverse association between blood pressure (BP) values and death in MHD patients (i.e., a high mortality rate has been paradoxically observed in MHD patients who have a low rather than a high predialysis BP, whereas high BP values have been shown to confer survival advantages) (**Klassen PS; et al , 2002**).

The Association between Blood Pressure and Mortality in ESRD

Similar to most physiologic parameters, blood pressure (BP) is associated with death risk at either extreme. Acutely, very low BP may decrease perfusion to vital organs while very high BP may lead to vascular damage and hemorrhages. Long term, high BP associated with concentric left ventricular hypertrophy, ventricular dilatation, ischemic heart disease, and CHF. However, after development of cardiac failure, low BP predicts mortality and is a potential marker for severity of cardiac disease (**Foley RN; et al 1996**).

Hence, it is possible that low BP in MHD patients is preceded by HTN and its CV consequences during early stages of chronic kidney disease although

mechanisms that maintain elevation of BP may fail gradually by the time the end stage renal disease is reached, the impaired CV system may persist. In addition, patients presenting with baseline predialysis hypotension may possess such subclinically significant risk factors or comorbidities as heart failure or ischemic cardiomyopathy (*Iseki K; et al 1997*).

However, some studies with large sample sizes have failed to find that high BP is an independent mortality risk factor in MHD patients. In a cross-sectional study of 936 MHD patients in the HEMO study, Cheung et al reported no significant association between predialysis systolic BP and any of the CV disease end points (*Cheung AK; et al 2000*). Also Iseki et al showed a strong association between low diastolic BP and risk of death in a cohort of 1243 MHD patients who were followed up for 5 years (*Iseki K; et al 1997*). Another study by Zager et al, in a study of 5433 MHD patients followed up for a mean of 2.9 years, noted that the relative death rate for patients with predialysis or postdialysis hypotension (systolic BP <110 mm Hg) increased to four times normal or 2.5 times normal, respectively (*Zager PG; et al 1998*).

A large study of cohort of 40 933 hemodialysis patients in the United States whose predialysis and postdialysis blood pressure values were recorded routinely during each hemodialysis treatment for 15 month. This study was carried by Kalantar-Zadeh; et al (2005), and it showed that the lowest mortality was associated with predialysis systolic pressure of 160 to 189 mm Hg, whereas normal to low predialysis pressure values were associated with significantly increased mortality. (*Kalantar-Zadeh K; et al 2005*).

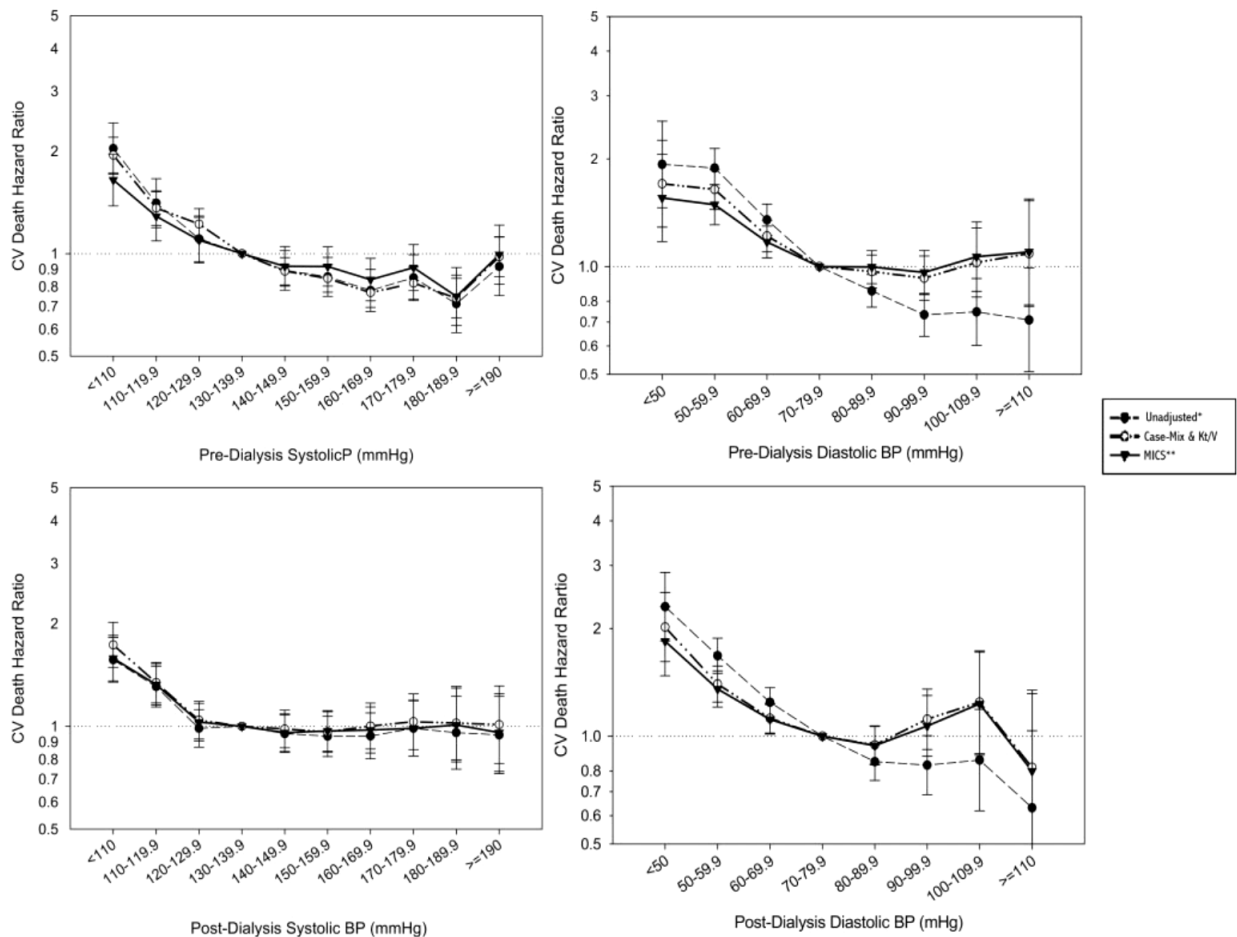


Figure 5. Association between BP and 15-month CV death in 40 933 MHD patients (95% confidence interval bars are depicted)

. Quoted from (Kalantar-Zadeh K; et al 2005).

Observational studies on hypertension in ESRD

Overview

One basic concern raised with observational studies is the perceived inaccuracy and high variability of BP measurements in HD patients. In one of these studies, automated BP was overestimated in dialysis patients by 14.3/ 7 mmHg when compared with a trained study nurse utilizing a standardized measurement technique.

. Such discrepancy is not surprising because many factors as

- The vascular access may limit BP measurement sites
- Immediate BP measurement upon arrival in the unit, especially if late (i.e., without a rest period).
- The patient may have smoked or ingested coffee prior to arrival in the unit.

Ambulatory blood pressure measurements (ABPM) have also been compared to BP obtained in the dialysis unit and up to 41% of patients had BP measured at 20/10 mmHg higher (mean: 25/13 mmHg) in the latter .

Therefore, a combination of factors may lead to overestimation of individual BP measurements in the dialysis units. To place this information in context, proponents of ABPM have criticized how inaccurate BP measurements in the general population have been for many years. The commonly cited error is a misdiagnosis of HTN, resulting from an overestimate of the BP of individual patients from the general population. (*Lazar AE; et al , 2004*)

overestimation of BP impact the interpretation of the evidence from observational studies in HD patients as Within the HD population, a simplistic approach supports the use of higher BP goals because an SBP of 160 mmHg may reflect a “true” SBP of 140 mmHg. Furthermore, because it is expected that the pre-HD BP is obtained at a point in time when the patient with adequate or compensated cardiac function is at the peak of intravascular volume, and should reflect one of the highest BP readings. (*Lazar AE; et al , 2004*). One way to decrease variability is to take multiple measurements, hence recommendations to take the BP in multiple

extremities, consider averaging two readings, and serial measurements when diagnosing and monitoring HTN. (*Lazar AE; et al , 2004*)

However, BP is obtained thrice weekly on most patients, is done both before and after HD treatments and when BP is reported in observational studies, they are usually averaged over a week, month, or quarter. Although such maneuvers do not eradicate variability and error, they do compensate toward a more accurate representation of the BP for many, but not all patients. (*Lazar AE; et al , 2004*).

Clinical Epidemiology

Very few studies of chronic dialysis patients have examined cardiovascular events and blood pressure values prospectively, with a long-term, longitudinal approach. In particular, the vast majority of studies have failed to use the careful, standardized methods used in high-quality, prospective studies like the Framingham Study. (*Agarwal R, 2005*) .

This is surprising, especially when one considers how variable pressure values can be in dialysis patients. One inception cohort study, which concluded over a decade ago, recorded blood pressure levels monthly and had a priori definitions for cardiac events; higher time-averaged blood pressure was a temporal antecedent of cardiac enlargement, ischemic heart disease, and, most especially, cardiac failure. The last of these was a portentous event that predated two-thirds of all deaths; cardiac failure was followed by falls in blood pressure and the degree of hypotension was the only predictor of mortality after cardiac failure. (*Li Z; et al , 2006*) .

Many other epidemiological studies relating blood pressure levels to mortality in dialysis populations have been published, and typically, these

differ markedly from those seen in general population settings. (*Stidley CA; et al , 2006*) .

These observations are certainly counterintuitive but in no way prove that hypertension is good for dialysis populations. However there is at least one potential scenario in which high blood pressure could truly cause bad outcomes and, yet, on average, an inverse association between blood pressure levels and mortality rates could be seen. In this situation, the statements that “hypertension increases mortality” and “normal blood pressure levels are associated with higher mortality rates” can both be true. In this scenario, the critical elements are the prevalence of the unmeasured co-morbidity and the fact that the unmeasured co-morbidity also leads to low blood pressure levels. (*Agarwal R, 2004*).

Observational studies have conflicting results with regard to the relationship between BP and mortality in patients with end-stage renal disease (ESRD), particularly those on HD. however The predominant finding of a high death risk associated with low BP as well as inconsistency in finding a similar association with high BP goes against the traditional view of high BP as one of the greatest modifiable risk factors for mortality in any population which is referred to reverse epidemiology.

Experimental Studies on hypertension in ESRD

Generally there is a feeling of discomfort when the proposition is advanced that observational evidence can be used to guide treatment decisions in dialysis populations. Despite their logistic difficulties and frequent problems with generalizability (reflecting the need for selected populations), it seems probable that only experimental studies, based on

randomly assigned treatment designs, can reliably inform treatment decisions.

One noteworthy study of limited numbers examined hemodialysis patients with left ventricular hypertrophy and hypertension with randomization to an angiotensin converting enzyme (ACE) inhibitor (perindopril) or a dihydropyridine calcium antagonist (nitrendipine) for one year. Although left ventricular hypertrophy regressed in both groups and blood pressure control was equivalent, more regression was seen in the ACE inhibitor treated patient. Another highly informative, although small, crossover trial compared short daily with standard, three times weekly hemodialysis. In spite of similar overall weekly urea clearance, blood pressure levels were lowered by daily dialysis, to the extent that antihypertensive medications were discontinued in most patients. Regression of left ventricular hypertrophy was observed. (*Fagugli RM; et al, 2001*)

Although definitive multicenter studies remain to be undertaken, an increasing number of smaller studies have accrued in recent years. (*Yu WC; et al, 2006, Takahashi A; et al, 2006*)

Although generally small, and with considerable degrees of heterogeneity (regarding patients, interventions, and outcomes), many of the studies suggest the possibility of benefit. Of particular importance, none of these studies suggest that antihypertensive treatment is intrinsically harmful in dialysis patients. The study of Zannad et al. is clearly the largest of those published to date. (*Fagugli RM; et al, 2001*)

This was a randomized, double-blind study of fosinopril or placebo in 397 hemodialysis patients with echocardiographic left ventricular hypertrophy,

whose primary outcome was the first occurrence of one of the following cardiovascular events—cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, coronary revascularization, heart failure, or cardiac arrest. Patients in the fosinopril group had a higher left ventricular mass index than those in the placebo group at baseline.

The composite cardiovascular event rate was 32.7% during the 2-year follow-up period. In the intent to treat analysis, there was no significant difference in the primary endpoint between the two groups (relative risk 0.93, 95% confidence interval 0.68–1.26, $p = 0.35$).

In a secondary analysis evaluating the per protocol data, there was a trend toward benefit for fosinopril (adjusted relative risk 0.795, 95% confidence interval 0.59–1.1, $p = 0.099$). Normotensive patients had no change in blood pressure, whereas hypertensive patients had 11.7 / 4.9 mmHg reduction, with fosinopril, compared with 5.4 / 2.1 mmHg with placebo. (*Agarwal R; et al , 2006*)

In the hypertensive group 19% of patients had BP <140 /90 mmHg in the placebo group and 35% in the fosinopril group. The differences in the baseline characteristics between the two groups and inclusion of normotensive patients in the study make extrapolation to a hypertensive population problematic. (*Agarwal R; et al , 2006*).

Table 11. Trials of antihypertensive strategies in dialysis populations

| Reference, n | Patients | Intervention | Follow-up (months) | Results |
|----------------------------|------------------------------------|--|--------------------|--|
| Zannad et al. n = 397 | HD, LVH | Fosinopril or placebo | 24 | Fosinopril had no effect on cardiovascular event rate |
| Cice et al. n = 144 | HD, dilated cardiomyopathy | Carvedilol or placebo | 12 | Regression of dilated cardiomyopathy and improved survival with carvedilol |
| Takahashi et al. n = 80 | HD | Candesartan or control | 19 | Reduction in cardiovascular event rate with candesartan |
| Ichihara et al. n = 64 | HD | Losartan, or trandolapril or placebo | 12 | Reduction in PWV with losartan and trandolapril |
| Yu et al. n = 46 | HD, normal BP | Ramipril, 2.5 mg 3 times/week, or placebo | 12 | No progression of LVH with low-dose ramipril |
| Shibasaki et al. n = 30 | HD, hypertension | Losartan or enalapril or amlodipine | 6 | Regression of LVH with losartan |
| London et al. n = 24 | HD, LVH, uncontrolled hypertension | Nitrendipine or perindopril | 12 | Regression of LVH with perindopril |
| Suzuki et al. n = 24 | CAPD, LVH | Valsartan or placebo | 12 | Regression of LVH with valsartan |
| Kanno et al. n = 24 | HD, diabetes, LVH | Losartan or placebo | 12 | Regression of LVH with losartan |
| Fagugli et al. n = 12 | HD, hypertension | Short daily or thrice-weekly HD, crossover | 6 | Regression of LVH with short daily hemodialysis |

HD, hemodialysis; LVH, left ventricular hypertrophy; CAPD, continuous ambulatory peritoneal dialysis; PWV, pulse wave velocity.

Quoted from Robert N. Foley and Rajiv Agarwal

The lack of standardization of blood pressure measurement in this patient population, and a lower than expected cardiovascular event rate may have reduced the power of the study to detect smaller, but meaningful, effects of fosinopril on cardiovascular disease rates. Once again, however, a key point to note was the lack of evidence suggesting net harm with antihypertensive treatment in dialysis patients. It is being increasingly recognized that blood pressures obtained within the dialysis unit are poor reflection of ambulatory blood pressures and better blood pressure measurements such as those obtained via self-measurement or ambulatory monitoring may improve diagnosis and treatment of hypertension. (*Agarwal R; et al , 2006*) .

When Is BP Too High or Too Low?

The goal of therapy, specifically the optimal BP target, remains debatable. The K/DOQI guidelines recommended treatment goals of <140/90 mmHg pre-HD and <130/ 80 post-HD (*National Kidney Foundation, 2005*). But does this BP goal fit all patients? At what level of high BP does the risk for mortality actually increase? How do we deal with the results of studies from

thousands of patients that indicate an association between low levels of BP and increased mortality risk? If we were to take a risk-averse stance, it is best to review the available evidence with regard to BP thresholds that are associated with higher risk of death.

Hypertension thresholds that have been associated higher mortality were handled by many studies (*Klassen PS; et al , 2002, Stidley CA; et al , 2006*).

However, the associated risk of death increases as systolic blood pressure (SBP) increases >160 mmHg pre-HD (most studies at >200 mmHg) and >154 mmHg post-HD (most studies at >180 mmHg). DBP of >90 mmHg diastolic pre-HD and >110 mmHg post-HD is also associated with increased death risk..

Therefore, the observational evidence supports a threshold for pre- HD SBP of up to 160 mmHg and DBP up to 90 mmHg on the high end without additional mortal risk. The associates for PP are less clear, especially as there is evidence for increased death risk associated with post-HD PP >60 mmHg but also for pre-HD PP<55 mmHg.

The lower BP thresholds that have been associated with higher mortality were also handled by many studies (*Li Z; et al , 2006, Kalantar-Zadeh K; et al , 2005*).

Table 9. High blood pressure (BP) thresholds associated with increased mortality risk in ESRD, predominantly on hemodialysis.

| Reference | Patient (n) | Reference (mmHg) | Threshold (mmHg) | Change in risk (%) | p-Value | Notes |
|-----------------------|------------------------------|------------------|------------------|--------------------|--------------------|------------------------------|
| SBP | | | | | | |
| Tomita et al. | 195 (incident) | <160 | ≥160 | N/A | N/A | Only two BP categories |
| Zager et al. | 5433 | 140–149 | >180 | +73 | 0.001 | Post-HD; Time-varying |
| Port et al. | 4499 | 120–149 | ≥180 | +32 | 0.06 | Post-HD |
| Foley et al. | 11,142 | ≤119 | >154 (post-HD) | +3 | 0.03 for trend | +3% per 10 mmHg |
| Li et al. | 69,590 and 56,338 (incident) | 160–179 | ≥200 | +52 and +27 | <0.0001 and 0.0341 | Time-varying |
| Stidley et al. | 16,959 | 140–149 | ≥150 | N/A | N/A | Subset with 3-year follow-up |
| DBP | | | | | | |
| Zager et al. | 5433 | 70–79 | ≥90 | +23 | N/A | 95% limits: 1.00–1.51 |
| Port et al. | 4499 | 70–89 | ≥110 | +125 | 0.04 | Post-HD |
| Kalantar-Zadeh et al. | 40,933 | 70–79 | ≥110 | +30 | 0.02 | Time-varying |
| HTN | | | | | | |
| De Lima et al. | 103 | ≤160/≤94 | >160/>94 | +122 | 0.026 | Mean age: 44 years |
| MAP | | | | | | |
| Fernandez et al. | 104 | ≤115 | >115 | +94 | N/A | MAP ~116 is BP ~160/95 |
| PP | | | | | | |
| Klassen et al. | 37,069 | 50–59 | ≥60 (post-HD) | +12 | <0.001 | 12% per 10 mmHg |

BP values were obtained pre-HD in prevalent patients unless indicated.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension defined by elevated SBP, DBP, or both; PP, pulse pressure; MAP, mean arterial pressure.

Quoted from Li Z et al, 2006.

The associated risk of death increases as SBP decreases <140 mmHg pre-HD (<160 mmHg in one study but the reference group was 160–179 mmHg). Post-HD, SBP <135 mmHg (most studies at post-HD SBP<110 mmHg) is associated with increasing death risk, with a steep increase in risk as SBP falls below 120 mmHg and lower. Diastolic BP of <70 mmHg diastolic pre-HD and post-HD is also associated with increased death risk, although two studies indicate improvement in risk at higher DB (*Blacher J; et al, 2002*).

Table 10. Low blood pressure (BP) thresholds associated with increased mortality risk in ESRD, predominantly on hemodialysis.

| Reference | Patient (n) | Reference (mmHg) | Threshold (mmHg) | Change in risk ^a (%) | p-Value | Remarks |
|----------------------------|-------------------|----------------------|---------------------------|---------------------------------|----------------------------|--|
| SBP | | | | | | |
| Zager et al. | 5433 | 140–149 | < 130 and > 150 and < 110 | +43 and –32 and +37 | 0.001 and < 0.01 and 0.001 | Pre-HD (linear risk) and post-HD; time-varying |
| Port et al. | 4499 | 120–149 | ≤ 109 | +86 and +28 | < 0.0001 and < 0.01 | Pre-HD and post-HD |
| Klassen et al. | 37,069 | 135–144 | < 135 | +13 per 10 mmHg | < 0.001 | Adjustment inc. PP |
| Kalantar-Zadeh et al. | 40,933 | 120–129 | post-HD < 120 and ≥ 130 | +17 and –11 | < 0.004 and 0.02 | Linear risk: less at high BP |
| Goldfarb-Rumyantzev et al. | 1053 PD patients | 111–120 | ≤ 110 and < 100 | +85 and +170 | < 0.005 and < 0.001 | Adjusted for Meds, LVH, CVD, etc. |
| Li et al. | 69,590 | 160–179 | < 160 | +11.1 and +22.4 | < 0.0001 (both) | Cox model and time-varying |
| | 56,338 (incident) | | < 140 and < 160 | +57.6 and +18.3 | < 0.0001 and 0.0005 | Cox model and time-varying |
| Stidley et al. | 16,959 | 140–149 | < 120 and < 140 | N/A | N/A | Cox model and time-varying |
| DBP | | | | | | |
| Iseki et al. | 1243 | < 69 | ≥ 70 | –16 per 10 mmHg | N/A | Lower risk at higher DBP |
| Zager et al. | 5433 | 70–79 | < 70 | +14 | < 0.05 | Post-HD |
| Blacher et al. | 241 | < 78 | > 94 | –40 | N/A | 95% limits: 0.3–1.0 |
| Foley et al. | 11,142 | ≤ 70.0 and ≤ 64.7 | ≥ 70.1 and ≥ 64.8 | –5 and –4 per 10 mmHg | 0.03 and 0.006 | Pre-HD and post-HD; less risk at high BP |
| Klassen et al. | 37,069 | 70–79 | < 70 | Post-HD 10 mmHg | +14% per < 0.001 | Adjustment inc. PP |
| Kalantar-Zadeh et al. | 40,933 | 70–79 | < 70 | +19 | < 0.0001 | Up to 100% higher risk at < 50 mmHg |
| HTN | | | | | | |
| Salem | 649 | ≥ 180/≥ 110 (severe) | < 160/ < 100 | +71 | 0.04 | Univariable analysis only |
| PP | | | | | | |
| Port et al. | 4499 | 65–73 | < 55 | +30 | 0.01 | |
| Stidley et al. | 16,959 | 70–74 | < 70 and < 65 | N/A | N/A | PP < 55 with +110% risk |
| MAP | | | | | | |
| Foley et al. | 432 | N/A | N/A | 36 | 0.009 | 36% per 10 mmHg fall |
| Salem | 649 | ≥ 106 | < 106 | +86 | 0.004 | Map ~ 106 is BP ~ 140/90 |

Quoted from Li Z et al, 2006.

Reverse epidemiology of serum cholesterol in ESRD

Introduction

Patients with chronic kidney disease have one of the highest risks for atherosclerotic complications known with a cardiovascular mortality 10- to 20-fold increased when compared with the general population. Several traditional and nontraditional risk factors contribute to this high risk. However, even large epidemiologic studies could not observe an association of these parameters with atherosclerotic complications or even observed the opposite which is known from the general population (*National Kidney Foundation, 2005*).

Lipid abnormalities in ESRD

Abnormalities in lipid metabolism occur in patients with chronic renal failure (including mild renal failure), on dialysis, and after renal transplantation (*Afzali B; et al, 2004*).

Overall, patients undergoing peritoneal dialysis are more likely to have an atherogenic lipid profile than those undergoing hemodialysis, this may be a direct consequence of the absorption of glucose from the dialysate solution (*Weiner DE, Sarnak MJ, 2004*).

The primary finding in chronic renal failure and dialysis is hypertriglyceridemia; the total cholesterol concentration is sometimes normal or low, perhaps due in part to malnutrition in some patients: (*Weiner DE, Sarnak MJ, 2004*).

1. Approximately 40 to 50 percent of patients with chronic renal disease and end-stage renal disease have triglyceride levels greater than 200 mg/dL (2.26 mmol/L).
2. Approximately 20 to 30 percent have total cholesterol levels greater than 240 mg/dL (6.2 mmol/L), while 10 to 45 percent have LDL cholesterol levels greater than 130 mg/dL (3.4 mmol/L).
3. In addition the dyslipidemia of ESRD is also characterized by an abnormal apolipoprotein (apo) profile with decreased concentrations of apo-A containing lipoproteins in HDL and increased concentrations of triglyceride-rich apo-B containing lipoproteins in very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL (*Attman P ; et al , 2003*).
4. Triglycerides are further enriched with apoC-III, such that the ratio of apoA-I to apoC-III is markedly reduced between the early stages of CKD and ESRD.
5. Reduced activity of the enzymes, lipoprotein lipase and hepatic lipase, as well as increased levels of apoC-III in VLDL, may explain the reduced clearance of these lipoproteins.

Lipoprotein (a) [Lp(a)] is structurally similar to LDL, but it contains an additional glycoprotein, apo-A. Lp(a) levels are elevated in ESRD and are typically higher in PD patients than in HD patients (*John Kevin Tucker , 2004*).

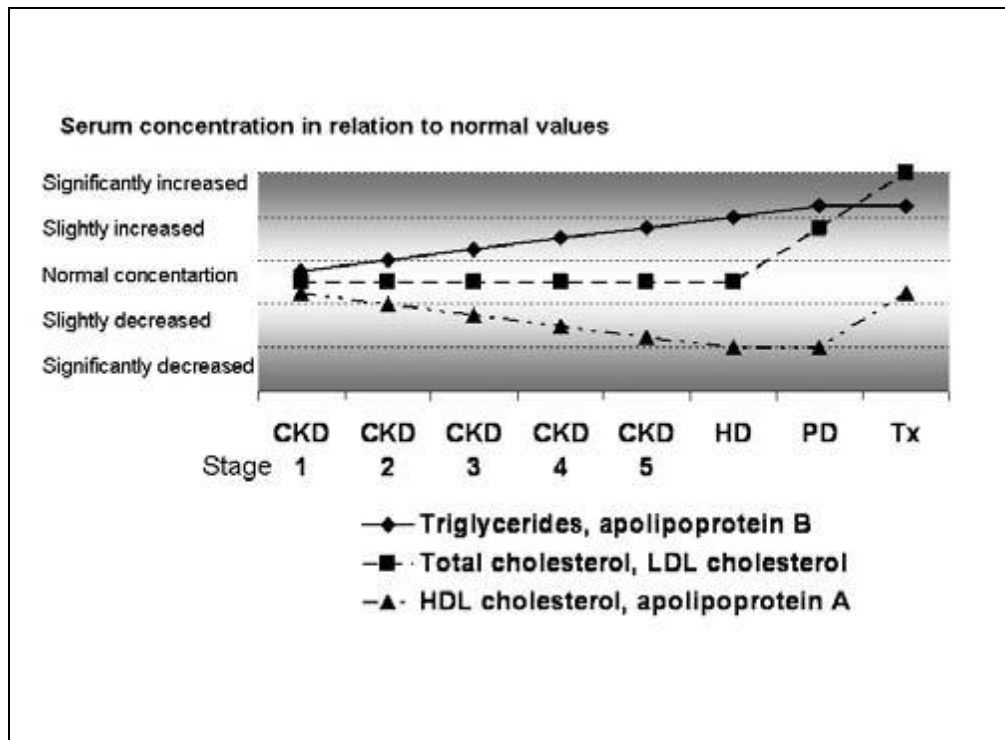


Figure 6. Simplified diagram of changes in lipid and apolipoprotein concentrations in the course of chronic kidney disease (CKD); HD = hemodialysis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PD = peritoneal dialysis; Tx = kidney transplantation.

Quoted from Michal Chmielewski; et al 2008.

Dialysis and dyslipidemia in ESRD

Initiation of dialysis treatment, however, may modify these lipid abnormalities through several mechanisms. Lipid profiles may be affected directly by the dialysis membrane. Seres et al compared pre and post dialysis lipid profiles among patients dialyzed with cellulosic membranes versus those dialyzed with polysulfone membranes and found that patients dialyzed with polysulfone membranes had significantly lower post-dialysis triglyceride concentrations, whereas levels did not change in those dialyzed with cellulosic membranes (*Attman P; et al , 2003*).

They hypothesized that lipoprotein lipase activity is increased with polysulfone dialyzers or an inhibitor of lipoprotein lipase is removed with a polysulfone dialyzer, but not with a cellulosic dialyzer. Other studies, however, have not demonstrated a significant difference in lipid profiles by dialyzer type (*Ottosson P; et al, 2001*).

Cholesterol and mortality in ESRD (Hypercholesterolemia paradox)

In patients receiving maintenance hemodialysis, reports suggest no relationship or paradoxical correlations, the so-called “reverse epidemiology,” where a lower total cholesterol level has been associated with a higher risk of death, (*Nishizawa Y; et al , 2001*) or conversely, a higher serum cholesterol level has been found in long-term dialysis survivors . These studies have often used registry data, and either all cause mortality or unspecified CV mortality. Similar inverse, “J” or “U”-shaped relationships between lipid levels and all cause mortality have been reported in other populations and are thought to reflect a high prevalence of co-morbid disease (specifically malignancy and associated malnutrition) in patients with low cholesterol levels.

It is likely that similar relationships are present in patients with advanced renal failure, further compounded by the atypical mix of CV outcomes in this population. These observations highlight the need for interventional trials and have led to under-treatment of dyslipidemia. Amongst patients starting dialysis, almost 40% are diabetic and 25% have known CAD, (*Nishizawa Y; et al, 2001*) and 30% of dialysis patients have cholesterol levels higher than 200 mg / dl (5.18 mmol/ l). Despite these observations,

and studies showing effective lipidlowering and safety of statins, less than 10% of patients commencing maintenance dialysis receive statins. (*Liu Y; et al, 2004*)

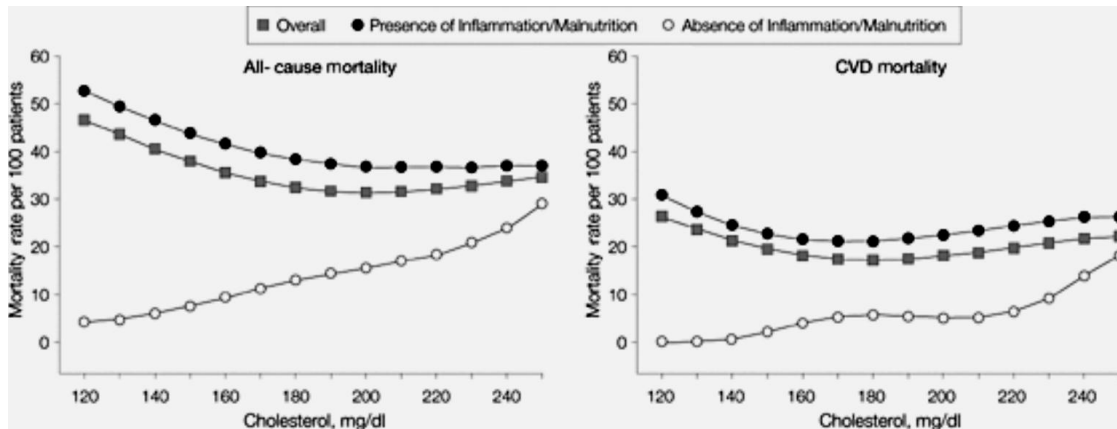


Figure 7. The relationship between total cholesterol and all-cause (left) or cardiovascular (right) mortality. The upper curves show the un-corrected “paradoxical” relationship, while the lower curve (open circles) shows the conventional relationship after correction for inflammation.

Quoted from Liu Y; et al, 2004.

The impetus now lies in clarifying the therapeutic benefit, and unravelling the mechanisms that underlie the cholesterol paradox.

Factors affecting Cholesterol paradox

The well-known association of high cholesterol levels with increased mortality in the general population was only observed in dialysis patients when no malnutrition/inflammation was present. If patients suffered from this condition, high cholesterol concentrations were associated with a better outcome which might be explained by the cholesterol-lowering effect of systemic inflammation and malnutrition (*Liu Y; et al, 2004*).

Besides this interaction with malnutrition and inflammation, many other factors might contribute to the reverse epidemiologic findings in dialysis patient.

1. when we are measuring low density lipoprotein cholesterol (LDL-C) or Lp(a) at a certain time during the progression of kidney disease, we get only a snapshot from that particular time which is not representative of the preceding and often longer-lasting time periods.
2. LDL-C is usually normal or even subnormal in hemodialysis patients and does not reflect possible long-lasting periods of the predialysis phase with markedly elevated LDL-C levels in case of a nephrotic syndrome. Knowing the area under the curve of LDL-C with time might probably be more informative (*Kwan BC; et al, 2007*).
3. Another reason for the negative findings might be that the measurement of LDL-C also includes the cholesterol derived from Lp(a). This could influence on epidemiologic studies as well as the calculation of the efficacy of therapeutic interventions. Furthermore, the atherogenic potential of dyslipidemia in kidney disease may depend more on the apolipoprotein than on lipid abnormalities, and may not always be recognized by measurement of plasma lipids alone (*Kronenberg F; et al, 2002*).
4. Finally, measured lipid or lipoprotein levels might not reflect their actual atherogeneity, which is markedly influenced by chemical modifications. These are, however, influenced, to a

large extent, by turnover and therefore production rate and residence time of these particles.

Metabolism of IDL and LDL in Hemodialysis Patients

Several mechanisms might contribute to the impaired metabolism of LDL and IDL in ESRD patients e.g.

1. Severe changes in enzyme functions and their cofactors
 - Decreased LCAT (lecithin cholesterol acyltransferase), LPL(lipoprotein lipase) and HTGL(hepatic triglyceride Lipase) activity leading to an impaired reversed cholesterol pathway.
2. Decreased clearance of LDL caused by
 - Chemical modification of LDL-apoB by oxidation, carbamylation and glycation (e.g., advanced glycation end products).
 - Increased triglyceride-to-cholesterol ratio.
 - Presence of small dense LDL.
 - Impaired binding to LDL receptor.
 - Reduction in LDL receptors.
3. Decreased production and prolonged residence time in hemodialysis patients.

One possibility is a contribution of LDL uptake by the healthy human kidney which is disturbed in chronic kidney failure. This is supported by the fact that glomerular cells such as mesangial or epithelial cells, at least in vitro, express lipoprotein receptors and to take up LDL comparably to fibroblasts and hepatocytes.

Whether the kidney plays a significant role in LDL catabolism in vivo is, however, unclear and is not supported by perfusion studies in rat kidneys

which showed that virtually no intact LDL is cleared from the circulation by the kidney (*Pegoraro AA; et al , 2002*).

Kinetics of Lp(a) in Hemodialysis Patients

Numerous studies in the general population have demonstrated that Lp(a) is a risk factor for cardiovascular disease (*Danesh J; et al , 2000*)

Lp(a) is an LDL-like lipoprotein consisting of apolipoprotein(a) [apo(a)] covalently bound to an LDL particle. Apo(a) shows a high homology with plasminogen and competes with this protein for binding to plasminogen receptors, fibrinogen, and fibrin. individuals with high molecular weight or large apo(a) isoforms have on average low plasma Lp(a) concentrations, while those with low molecular weight or small isoforms usually exhibit high plasma Lp(a) concentrations. Depending on the population under investigation, this association explains between 30% and 70% of the variability in plasma Lp(a) levels (*Danesh J; et al , 2000*).

In kidney disease, plasma Lp(a) levels are significantly influenced by the glomerular filtration rate (GFR). In patients with large apo(a) isoforms, but not for those with small apo(a) isoforms, plasma Lp(a) levels begin to increase already in the earliest stages of renal impairment before GFR starts to decrease (*Kronenberg F; et al , 2000*).

Thus, the elevation of Lp(a) in chronic kidney disease is an acquired abnormality, mostly influenced by the impaired GFR and the degree of proteinuria and less by the cause of kidney disease. Malnutrition and inflammation have also been associated with high plasma Lp(a) levels in hemodialysis patients. It seems that inflammation only modifies Lp(a)

concentrations, but fails to explain the apo(a) phenotype-specific elevation of plasma Lp(a). Recently performed in vivo turnover studies using stable isotope techniques which elucidated the mechanism for the increased plasma Lp(a) levels in hemodialysis patients, showed that production rates of apo(a) and apoB, the two apolipoproteins contained in Lp(a), were normal when compared with control subjects with similar plasma Lp(a) concentrations (*Frischmann ME; et al , 2007*).

The fractional catabolic rate of these apolipoproteins was, however, significantly reduced compared to controls. This resulted in a much longer residence time in plasma of almost 9 days for apo(a), compared to only 4.4 days in controls. This decreased clearance of Lp(a) results in increased Lp(a) plasma concentrations and is likely the result of loss in kidney function and not increased production in hemodialysis patients. A role of the kidney in the catabolism is supported by arteriovenous differences of Lp(a) concentrations between the human arterial and renal vein (40) as well as by apo(a) fragments in urine.

The turnover study in hemodialysis patients points to fundamental differences in the metabolism of Lp(a) and other proteins in these patient groups. As the fractional catabolic rate of albumin in hemodialysis patients is similar or even reduced compared with controls (*Giordano M; et al, 2001*).

The observation of markedly decreased FCR of apoB of LDL and IDL as well as apo(a) and apoB in Lp(a) causes a prolonged retention time of these highly atherogenic lipoproteins. Due to the long retention period “aged” lipoprotein complexes are thus more susceptible to alterations such as

oxidation damage, which was shown to be associated with accelerated atherogenesis in hemodialysis patients and this pose an additional risk factor for the increased incidence of cardiovascular disease in hemodialysis patients (*Shoji T; et al , 2002*).

Dyslipidemia or Hyperlipidemia

While certain atherogenic lipid abnormalities are present in ESRD patients, levels of total cholesterol and LDL cholesterol can be actually lower than those of persons without renal failure. The power of non-HDL-C as a predictor of CV mortality was investigated in a cohort of 525 Japanese hemodialysis patients (*Nishizawa Y; et al, 2003*).

This is important as non-HDL-C is a marker that integrates atherogenic potentials carried by VLDL, IDL and LDL. Non-HDL-C was been shown to be a significant and independent predictor of CV mortality, despite that the Japanese population in this study is undoubtedly healthier than the US dialysis population, with much lower annual mortality rates, 4.6% vs. 20%. (*Liu Y; et al, 2004*)

Thus, the notion that hyperlipidemia is not harmful and even protective in ESRD may also be flawed by the tendency to look at hypercholesterolemia rather than dyslipidemia. “Uremic dyslipidemia” involves quantitative and qualitative changes in a variety of lipid sub fractions that may contribute to premature CVD (and CAD in particular), even though total and LDL cholesterol levels are low (*Chang JW; et al, 2002*).

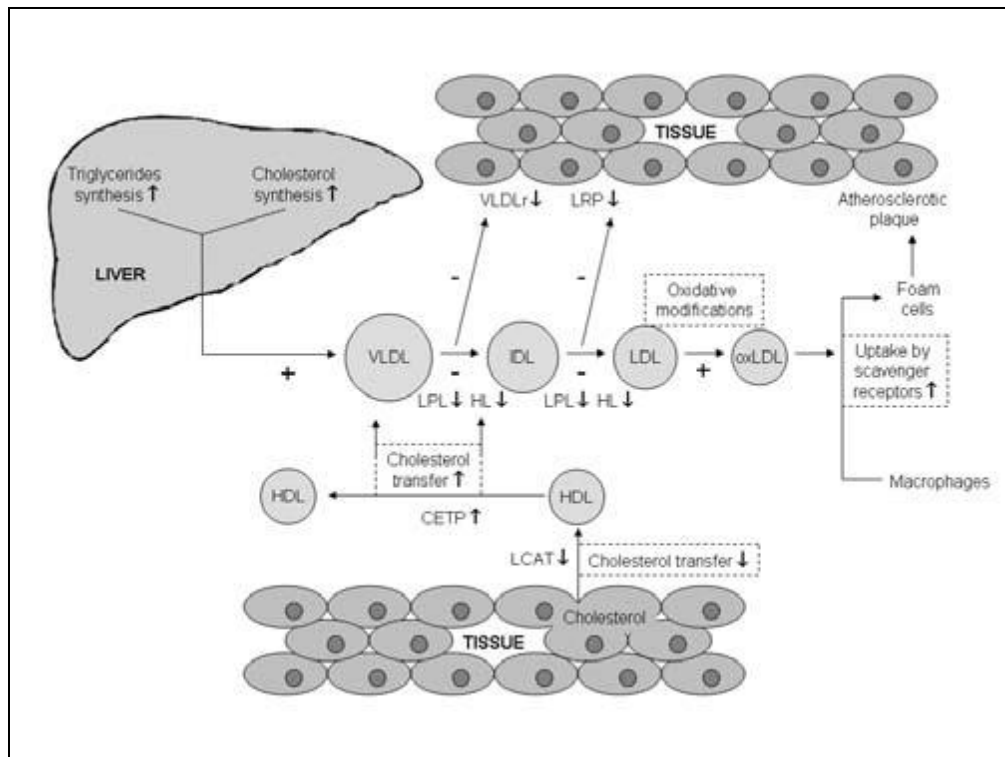


Figure 8. Major disturbances of lipoprotein metabolic pathways in the course of CKD. CETP = cholesterol ester transfer protein; HDL = high-density lipoproteins; HL = hepatic lipase; IDL = intermediate-density lipoproteins; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoproteins; LPL = lipoprotein lipase; LRP = LDL receptor-related protein; oxLDL = oxidized LDL; VLDL = very low density lipoproteins; VLDLr = VLDL receptor.

Quoted from Michal Chmielewski; et al 2008.

The beneficial effects of statins, and other agents, on such patterns of dyslipidemia and associated factors, such as oxidized LDL cholesterol, and their established beneficial effects on biomarkers of subclinical atherosclerosis suggest that lipid lowering is likely to have beneficial effects on CVD in this population (*Calabro P, Yeh ET, 2005*).

So it was proposed that patients with CKD should be considered to be in the highest risk category, with a target LDL-C level for CKD patients below 100 mg/dL. Statin treatment is recommended as first-line drug therapy for high LDL and non-HDL cholesterol levels in patients with CKD, in addition to therapeutic lifestyle changes.

A retrospective analysis of data of 3716 patients from the USRDS Dialysis Morbidity and Mortality Wave 2 study (*Seliger SL; et al , 2002*) showed that statin use is associated with an independent reduction in CV mortality.

Indirect evidence to support the use of statins comes from The Assessment of Lescol in Renal Transplantation (**ALERT**) study of ESRD patients with renal transplants (*Holdaas H; et al, 2003*)

In this multicentre, randomized, double- blind, placebo-controlled trial of fluvastatin treatment in 2102 transplant recipients. Fluvastatin successfully lowered mean LDL cholesterol, total cholesterol, and triglyceride levels without side effects. Like the 4D study, the composite primary end-point was reduced, but not significantly, although there was a statistically significant reduction (of about a quarter) in the risk of MI. In a 7–8 year follow-up (*HoldaasH; et al , 2005*), of this study group, patients initially randomly allocated to statin therapy had a significant reduction in cardiac events; the composite end-point of cardiac death and nonfatal MI was 29% lower in the fluvastatin treatment arm, similar to the effects seen with statin treatment in other populations. (*Qunibi WY., 2005*)

The mechanisms for the development of CAC have still not been fully elucidated. In a study by Chertow (**Chertow GM; et al, 2002**), patients receiving the phosphate-binder sevelamer had a significant decrease in plasma LDL-cholesterol levels (sevelamer being an anion exchange resin that binds cholesterol and bile acids) and reduced CAC and aortic calcification.

Reverse Epidemiology of Plasma Total Homocysteine

Introduction

Among several CV risk factors, the markedly increased level of plasma total homocysteine (tHcy) in ESRD patients has been suggested as one independent risk factor for CVD. (*Wald DS; et al, 2002*).

However, not all prospective cohort studies are consistent with this finding (*Homocysteine Studies Collaboration, 2002*) The suggestion about 40 years ago that homocysteine (Hcy) may be linked to cardiovascular disease (CVD) was based on the observation that subjects with homocystinuria, an inborn error of the enzyme cystathionine b-synthase, are prone to develop severe atherogenic and thrombotic arterial disease (*Kaul S; et al, 2006*).

Subsequently, several epidemiological studies have suggested that even a mildly elevated plasma total homocysteine (tHcy) is an independent and graded risk factor for CVD in the general population. Notably, whereas this association was reported in studies with a retrospective and cross-sectional design, much weaker, or even absent, correlations were reported in prospective studies. This discrepancy raised the question whether mild-moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis or just an innocent by stander (*Homocysteine Studies Collaboration, 2002*).

Relationships between high tHcy levels and CVD as well as worse survival have been reported in ESRD patient. Mallamaci, et al (2002) have recently reported in a cohort of patients with ESRD an association between

high tHcy and incident CV events independent of traditional and non-traditional risk factors, such as serum C-reactive protein (CRP) and hypoalbuminaemia. In contrast, recent studies in ESRD patients show that a high tHcy concentration is not associated with CVD and in fact is a predictor of improved survival in ESRD (*Wrone EM; et al, 2004*).

Chronic Kidney Disease and Hyperhomocysteinemia

Chronic kidney disease (CKD) is one of the most frequent causes of hyperhomocysteinemia and when the renal insufficiency reaches the stage when dialysis treatment is initiated, more than 90% have a moderate degree of hyperhomocysteinemia ($>15 \text{ } \mu\text{mol/l}$) (*Suliman ME; et al, 2005*)

As a meta-analysis by Wald et al, (2002) showed that a $5 \text{ } \mu\text{mol/l}$ increase in tHcy was associated with a 32% higher risk of cardiovascular events, the increased Hcy levels observed in CKD patients could be considered clinically significant. Thus, as hyperhomocysteinemia is such a common phenomenon in uremic patients, it was suggested to be one important underlying cause of the unacceptable high cardiovascular risk in this patient population (*Suliman ME; et al, 2005*).

Clearly, some of the studies investigating the association between high tHcy and worse outcome in CKD patients are subject to some restrictions. Menon et al. (2006) examined the link between tHcy levels and outcomes in a cohort of 804 patients with CKD stages 3–4. Although their study showed an association between high tHcy and all-cause and cardiovascular mortality in “unadjusted” analyses this association was largely mitigated by adjustment for renal function. As it has been reported that Hcy induces mesangial cell apoptosis, it could be speculated that Hcy may be a risk factor

for progression of CKD and thereby as a secondary effect promote the development of CVD. In accordance with this concept, tHcy was found to be a predictor of the development of microalbuminuria in nondiabetic individuals independent of glomerular filtration rate (GFR) (*Jager A; et al, 2001*) .

Furthermore, Ninomiya et al. (2004) showed a significant inverse association between the baseline tHcy level and rate of change in kidney function during 5 years, even after adjustment for GFR. Taken together, these findings raise the question that prior studies performed in the general population, demonstrating an association between Hcy and CVD risk have inadequately adjusted for the confounding effects of reduced GFR.

Table 11. Summary of clinical studies on plasma total homocysteine (tHcy) showing positive associations with clinical outcome in chronic kidney disease patients

| Study | Study type | Number and category | Conclusions |
|------------------------|-------------------------|---------------------|--|
| Chauveau et al. 1993 | Cross-section | 118 HD | tHcy was higher in pts with occlusive arterial disease |
| Backmann et al. 1995 | Cross-section | 50 HD | tHcy was associated with occlusive arterial disease |
| Robinson et al. 1996 | Cross-section | 176 ESRD | Pts with tHcy level in the upper two quintiles, vs lower three quintiles, had OR of 2.9 for CV events |
| Jungers et al. 1997 | Cross-section | 93 CKD | tHcy was an independent risk factor for CV events |
| Kunz et al. 1999 | Cross-section | 63 HD | OR for past CV events was 12.6 comparing pts in the highest quartile vs. lowest tHcy quartile |
| Bostom et al. 1997 | Prospective (17 months) | 73 HD | Pts with tHcy level in the upper quartile, vs. lower three quartiles, had OR of 3.0 and 4.4 for nonfatal and fatal CVD, respectively |
| Moustapha et al. 1998 | Prospective (18 months) | 176 ESRD (130 HD) | The OR for CV events increased 1% per $\mu\text{mol/l}$ increase in tHcy. |
| Dierkes et al. 2000 | Prospective (24 months) | 102 HD | Higher tHcy associated with all-cause mortality, but not with CV events |
| Ducloux et al.* 2002 | Prospective (41 months) | 240 PD | High tHcy level as well as high CRP and low s-albumin levels were risk factors for CV events |
| Mallamaci et al.* 2002 | Prospective (29 months) | 175 HD | The OR for fatal and nonfatal atherothrombotic events was 8.2 times higher in pts with tHcy level in tertile 1 vs. tertile 3 (lower) |
| Kronenberg et al. 2003 | Prospective (12 months) | 155 ESRD (105 HD) | tHcy was related to the progression of arterial calcifications |
| Buccianti et al. 2004 | Prospective (44 months) | 77 HD | One $\mu\text{mol/L}$ increase in tHcy was associated with 3% increase in mortality |
| Mallamaci et al. 2005 | Prospective (44 months) | 205 HD | High tHcy was associated with vascular access thrombosis |
| Tsai et al. 2005 | Cross-section | 109 HD | tHcy is a predictor for arterial stiffness and pulse pressure |
| Anan et al. 2006 | Cross-section | 44 HD | tHcy is an independent risk factor for silent cerebral infarction |

(Quoted from Mohamed E et al; 2007)

Table 12. Summary of clinical studies on plasma total homocysteine (tHcy) showing inverse or no associations with clinical outcome in chronic kidney disease patients

| Study | Study type | Number and category | Conclusions |
|-----------------------------|---|---------------------------|---|
| Vychytil et al.* 1998 | Cross-section | 154 PD | No significant difference in tHcy level between PD pts with or without CVD |
| Sirrs et al. 1999 | Cross-section + prospective (9 months) | 96 HD 88 HD | tHcy was an inverse independent predictor of previous vascular access failure; pts with higher tHcy had a better survival rate |
| Suliman et al.* 2000 | Cross-section + Prospective (36 months) | 117 HD | Pts with CVD had low tHcy; tHcy level was influenced by nutritional status; pts with higher tHcy had a better survival rate |
| Wrone et al.* 2001 | Cross-section | 459 ESRD (430 HD) | tHcy was an inverse independent predictor of the presence of CVD |
| Suliman et al.* 2002 | Cross-section | 151 CKD | Lower tHcy was associated with presence of CVD; tHcy level was influenced by the nutritional status |
| Bayés et al.* 2003 | Prospective (24 months) | 94 HD | CRP, but not tHcy or S-albumin, was a risk factor for mortality |
| Wrone et al.* 2004 | Prospective (24 months) | 510 ESRD (468 HD) | Higher tHcy was associated with fewer CV events; supplementation of folic acid did not affect event rates |
| Kalantar-Zadeh et al.* 2004 | Prospective (12 months) | 367 HD | Lower tHcy was associated with increased hospitalization and the OR for death for the lowest tHcy quartile was 2.3 compared with the upper three quartiles |
| London et al. 2004 | Prospective (60 months) | 78 HD | tHcy was not associated with all-cause mortality |
| Suliman et al.* 2004 | Cross-section + Prospective (48 months) | 250 CKD | Low tHcy was associated with inflammation and poorer survival |
| Busch et al. 2004 | Prospective (26 months) | 232 CKD | Low tHcy was associated with CV events |
| Leskinen et al. 2004 | Cross-section | 136 CKD | No association between tHcy and CIMT |
| Friedman et al. 2005 | Prospective (2.6 year mean follow-up) | 1575 diabetic nephropathy | No association between tHcy and CVD outcomes |
| Wang et al. 2005 | Prospective (35 months) | 160 PD | tHcy was not associated with increased risk for overall death and fatal and nonfatal CV events |
| Ravani et al. 2005 | Prospective (27 months) | 131 CKD | Increase in tHcy did not predict event occurrence for progression of ESRD and mortality |
| Nair et al. 2005 | Cross-section + prospective (6 months) | 147 HD | No difference in tHcy level between pts with or without CVD; the rate of ischemic events was not related to tHcy levels |
| Ducloux, et al.*# 2006 | Prospective (54 months) | 459 HD | High tHcy inversely associated with risk for all-cause and CV mortality in patients with inflammation-wasting and positively associated in patients who do not present inflammation wasting |
| Menon et al. 2006 | Prospective (120 months) | 804 CKD | High tHcy was not a risk factor for all-cause or CV death |
| Suliman et al. 2006 | Prospective (12 months) | 63 CKD | Changes in CIMT during 1 year on dialysis treatment were not associated with tHcy levels |
| Zoungas et al. 2006 | Prospective (3.6 years) | 315 CKD | tHcy did not associate; high-dose folic acid did not slow atheroma progression or improve CV morbidity or mortality |
| Kumagai et al. 2006 | Cross-section + Prospective (60 months) | 197 HD | Neither high nor low tHcy was associated with atherosclerotic indices or CV events |
| Suliman et al. 2007 | Prospective (66 months) | 317 CKD | Low tHcy was associated with higher all-cause and CV mortality; adjustment for inflammation wasting showed a trend toward increased death risk for high, rather than low, tHcy |

Studies that include an evaluation of inflammation wasting, as confounding factors for tHcy. The study had a positive association in patients with no inflammation wasting.

(Quoted from Mohamed E et al; 2007)

Homocysteine induced Vascular Disease

In the absence of strong epidemiologic evidence linking Hcy to CVD the causal relationship between these factors may be weak. Indeed, there are several indirect mechanisms by which hyperhomocysteinemia may promote atherosclerosis.

First, Liao et al. (2006) and Mikael LG; et al, (2006) found that Hcy reduces the concentration of HDL-cholesterol in plasma by inhibiting the hepatic synthesis of apoA-I. and this may be one indirect mechanism by which Hcy may contribute to the development of atherosclerosis.

Second, Hcy may be biologically related to other potential risk factors for CVD, such as S-adenosyl homocysteine (SAH), adenosine and cysteine (thiol compounds that are elevated in CKD patients).Consequently, it could be speculated that Hcy does not by itself cause vascular damage, but that a high level of Hcy is merely a marker biologically related to other thiol risk factor(s), or alternatively that Hcy may work in concert with them .However, the consequences of altered thiol metabolism in CKD remain indecisive and there is no study as yet describing the interrelationship between these different thiol compounds and their relationship with atherosclerosis in CKD patients. (*Riksen NP; et al, 2003*).

Third, it has been suggested that the reduced form of Hcy, rather than tHcy, may be the Hcy fraction that exerts the toxic effects on the vasculature. In addition, it should be emphasized that changes in genomic DNA methylation may have important regulatory functions in normal and pathological cellular processes, such as atherosclerosis.

Association Studies between Hcy and Outcome in CKD

It is puzzling that whereas hyperhomocysteinemia is significantly associated with CVD in some studies it does not show up as a risk factor for CVD in others. Several possible explanations may explain this discrepancy, including survival bias, different inclusion criteria and temporal discrepancies between competitive risk factors. (Kalantar-Zadeh K; et al , 2004).

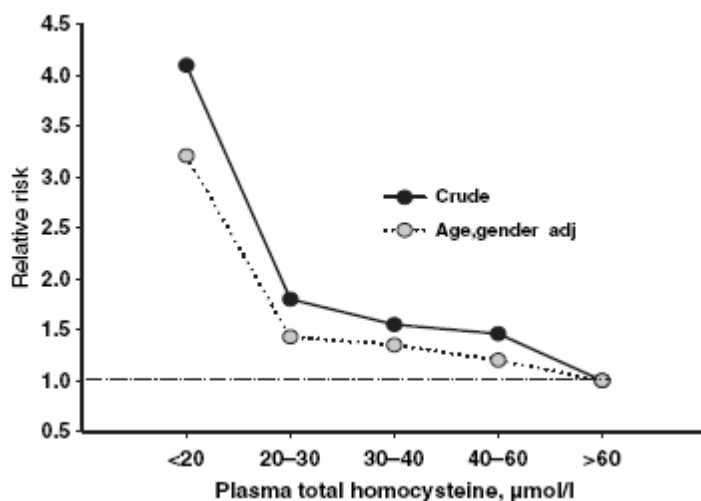


Figure 9. Reverse association of plasma total homocysteine (tHcy) with all-cause mortality in 695 patients with chronic kidney disease stage 5. Low tHcy levels (<20 µmol / l) showed higher hazard ratio for mortality, compared to other tHcy groups (>20 µmol), in nonadjusted and adjusted (age and gender) analyses.

(Quoted from Mohamed E Suliman et al, 2007)

It should be emphasized that several commonly occurring complications, such as inflammation and protein-energy malnutrition (PEM), may influence circulating tHcy levels in the uremic milieu. Notably, these two conditions, which often occur concomitantly in CKD and predict poor outcome, are both associated with hypoalbuminemia. (Kalantar-Zadeh K; et al , 2003).

Circulating tHcy exists mainly as protein-bound form with albumin being the main Hcy binding protein, and this is reflected by a strong positive association between plasma tHcy and serum albumin. In a longitudinal follow-up study in CKD patients for 12 months during dialysis treatment, we found a strong correlation not only between baseline levels of tHcy and S-albumin but also between changes in tHcy and S-albumin levels. (*Suliman ME; et al , 2005*).

As previous studies showed that plasma tHcy is lower in CKD patients with PEM and inflammation , and epidemiological studies have shown a strong association between clinical outcomes and both PEM and inflammation in CKD patients, it has been suggested that PEM and inflammation (via hypoalbuminemia) might be confounders for the apparent reverse association between tHcy and clinical outcome. (*Suliman ME; et al , 2006*).

Ducloux et al. (*Ducloux D; et al , 2006*) evaluated whether the association between tHcy and mortality would eventually be altered by the presence of PEM and inflammation in 459 HD patients. They found that tHcy was not significantly associated with a higher risk of death in the overall patient population. However, when patients were divided into two groups based on the state of PEM inflammation, tHcy tended to be inversely related to all-cause death rate in PEM-inflamed HD patients; whereas, an opposite association was found in HD patients without PEM or inflammation.

In accordance, we showed in 317 CKD stage 5 patients that the inclusion of several confounders known to be associated with tHcy (age, gender, GFR, and plasma folic acid) or well-established risk factors in the general population (serum cholesterol, blood pressure, CVD, and diabetes mellitus)

did not alter the relationship between tHcy and outcome. However, following the adjustment for the presence of PEW and inflammation, a high tHcy was associated with higher mortality than a low tHcy in this group of CKD patients. Taken together, these results suggest that the presence of PEW inflammation in large part account for the observed reverse association between tHcy and clinical outcome in CKD patients. (*Suliman M; et al , 2007*).

Chronic kidney disease may be one of the clinical situations in which the presence of a reverse epidemiology is most persuasive (60). In CKD patients, various risk factors, from hyperhomocysteinemia to serum cholesterol level, blood pressure, body weight, and other factors, are related inversely to death and CV complications. (*Kalantar-Zadeh K; et al , 2003*).

Although this inverse association initially was taken as a proof that high tHcy levels should not be implicated in the high risk of these patients, analyses based on CKD cohorts that excluded patients with PEM and inflammation clearly showed that tHcy level is related directly to incident CV events. Thus, the presence of inverse epidemiology may not necessarily imply that the principles of vascular pathophysiology are different in CKD patients but rather indicate that other superimposed factors, such as PEW and inflammation, are more important. Epidemiologic studies in the general population show that a modest elevation of tHcy concentration from 15 to 20 $\mu\text{mol/L}$ contributes to atherosclerotic vascular disease. If this graded relation reflects a pathogenic role of Hcy in the development of CVD one could assume that mild hyperhomocysteinemia would, indeed, be associated with increased cardiovascular risk also in the CKD population.

As the problem of confounding cannot be solved in epidemiologic studies regardless of what is thought to be an adequate adjustment, Mendelian randomization could be a new approach for interpretation of results and excluding confounders as an explanation for reverse association. (*Zoccali C; et al, 2006*).

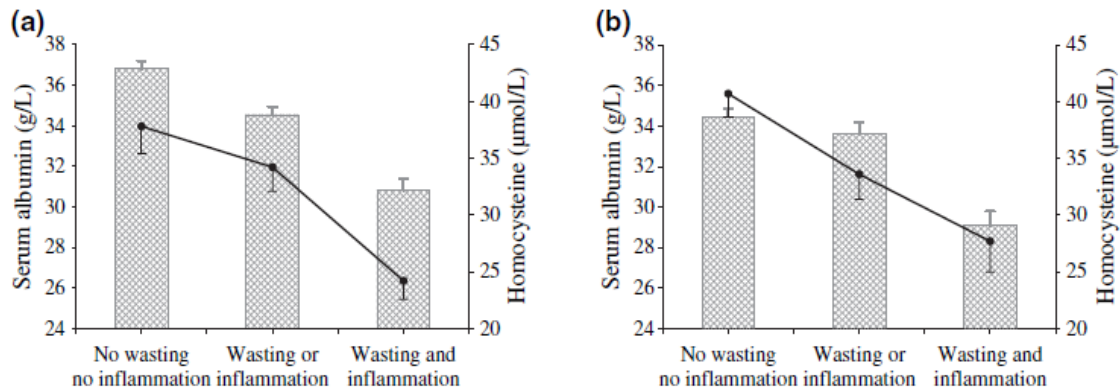


Figure 10. Influence of protein energy wasting (PEW; as defined by subjective global assessment score >1) and inflammation (C-reactive protein ≥ 10 mg / l) on total homocysteine (tHcy) (solid lines) and serum albumin (boxes) concentrations in 228 hemodialysis (HD) patients. (a) and 345 nondialyzed chronic kidney disease (CKD) stage 5 patients (b). The patients were divided into three groups based on the presence of PEW and / or inflammation. PEW and inflammation cause reduction in tHcy levels in HD and nondialyzed CKD patients. The presence of both PEW and inflammation was associated with a more marked decrease in tHcy level than the reduction caused by the presence of only one of these risk factors.

(Quoted from Stenvinkel P et al; 2000).

Effect of lowering total homocysteine on Cardiovascular Events

There are three recent large controlled randomized trials (*Lonn E; et al, 2006*) that indicate that lowering of tHcy levels does not reduce cardiovascular events in patients with existing CVD.

In the Vitamin Intervention for Stroke Prevention trial (*Toole JF; et al, 2004*) 3680 patients were randomized to high or low doses of folic acid,

vitamin B6 and vitamin B12 after ischemic stroke. The results showed that a moderate reduction in the tHcy level had no significant effect on vascular outcomes over a follow-up period of two years.

In the Heart Outcomes Prevention Evaluation (HOPE) second trial, 5522 adults with vascular disease or diabetes were randomized to either a combination of B vitamins or placebo. During 5 years of follow-up there was no significant benefits for the primary composite outcome of death from cardiovascular causes, myocardial infarction, and stroke were found in this study (*Bonaa KH; et al, 2006*).

Finally, the Norwegian Vitamin Trial included 3749 patients with a recent acute myocardial infarction. During 3 years of follow-up, mean plasma tHcy levels decreased by 27% in the group that were given folic acid plus B12, but did not change in the two groups that received vitamin B6 alone or placebo. There was no statistically significant reduction in cardiovascular events or total mortality in the group that was given folic acid and vitamin B12 compared with the group not given folic acid and vitamin B12. Notably, compared with the placebo group, the group given folic acid, vitamin, and B12 had an unexpected increased risk for the primary outcome and for myocardial infarction (*Lonn E; et al, 2006*).

In accordance with those results in patients without kidney disease, Wronne et al.(2004) showed in 510 dialysis patients that administration of high-dose folic acid, with a median duration of 24 months treatment, did not affect event rates. Moreover, in the Atherosclerosis and Folic Acid Supplementation Trial, 315 CKD patients were randomized to 15 mg folic acid daily or placebo and followed for a median of 3.6 years. Although tHcy

was reduced by 19%, folic acid did not appear to slow the atheroma progression rate or improve cardiovascular morbidity or mortality in this group of patients (*Zoungas S; et al, 2006*).

Although folic acid is the most investigated intervention to reduce plasma homocysteine, it should not be overlooked that there is experimental evidence that this otherwise precious vitamin might be a mixed blessing as far as cardiovascular risk is concerned. Folate stimulates cell proliferation and by this mechanism may in theory promote in a direct way the progression of atherosclerosis. Furthermore, the increased methylation potential prompted by folic acid on one side facilitates homocysteine disposal but may also promote DNA hyper-methylation and the transformation of l-arginine into Asymmetric Di Methyl Arginine (ADMA), i.e., two processes that may trigger or exacerbate atherogenesis (*Zoccali C,2006*).

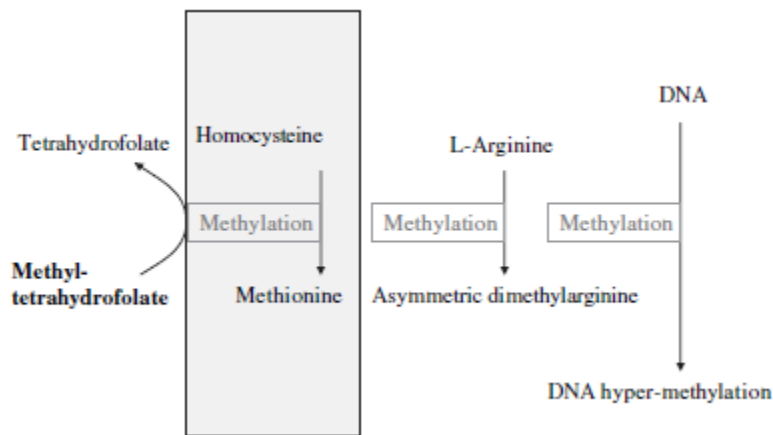


Figure 11. Methyltetrahydrofolate availability favors methylation of homocysteine to form methionine (a favorable process, gray area) but methyl groups availability may also increase the generation of asymmetric dimethylarginine (a nitric oxide synthase inhibitor) and promote DNA hyper-methylation, i.e., two pro-atherogenic processes.

(Quoted from Lund G et al; 2004)

Also some studies showed that enough folic acid is not the only option to lower homocysteine. N-acetylcysteine (NAC), a thiol-containing compound, is a potent homocysteine lowering agent particularly when administered intravenously across dialysis in ESRD. Indeed, it brings plasma homocysteine to levels as low as 2.2 μ M post dialysis with sustained benefits also in the dialysis interval (*Scholze A; et al, 2004*).

Interestingly, NAC triggered changes in plasma homocysteine across dialysis are associated with a decrease in pulse pressure and with improved endothelial function. These associations suggesting a favorable effect of homocysteine lowering go along with the results of a randomized, placebo-controlled, clinical trial where NAC administered by oral route produced a 40% reduction in the risk of cardiovascular events in hemodialysis patients. However, homocysteine plasma levels were not reported and no effect on all cause-mortality was registered in this study (*Tepel M; et al, 2003*).

Homocysteine and Mortality in ESRD

Although multiple studies have addressed the question whether tHcy may contribute to, or predict, cardiovascular events or mortality in CKD patients, there is not yet any conclusive answer to this important question.

As malnutrition and inflammation are thought to significantly contribute to the unacceptably high mortality rate of up to 10–20% per year in this patient population, it is possible that nutritional and/or anti-inflammatory interventions will improve clinical outcome in dialysis patients. (*Scholze A; et al, 2004*)

Also, recent data suggest that folic acid has the capacity to promote rather than inhibit atherothrombosis, (*Loscalzo J, 2006*) overriding the potential benefits derived from Hcy lowering. This could possibly explain the multiple negative trial results with folic acid supplementation. Future studies are needed to evaluate if thiol exchange agents, such as acetylcysteine and mesna (*Urquhart BL; et al , 2007*), may be a part of a future multifactorial intervention regime targeting inflammation, wasting, oxidative stress as well as hyperhomocysteinemia in this high-risk patient population (*Zoccali C, Mallamaci F, 2006*).

We still need well-powered intervention studies aimed at establishing whether lowering plasma homocysteine produces beneficial effects in dialysis patients. Trials based solely on folic acid are probably inadequate to test the hypothesis. Alternative approaches can be now envisaged. Accepting the conclusion that the homocysteine pathway cannot be used for interventions aimed at curbing cardiovascular risk is, at least by now, unwarranted (*Zoccali C 2006*).

Other possible examples of reverse epidemiology

A. Serum creatinine

In the general population, a slight or moderate increase in serum creatinine has been shown to be an independent risk factor of cardiovascular disease (*Ruilope LM; et al, 2001*).

A secondary analysis of the HOPE Study showed that in patients who had either preexisting vascular disease or diabetes mellitus and an additional cardiovascular risk factor, the presence of mild renal insufficiency significantly increased the risk for subsequent cardiovascular events (*Mann JF; et al, 2001*).

The HOT Study showed that a baseline elevation in serum creatinine is powerful predictors cardiovascular events and death (*Ruilope LM; et al, 2001*). In dialysis patients, the serum creatinine, a reflection of muscle mass or meat ingestion and/or the degree of dialysis efficiency, has also been shown to be a predictor of mortality but in the opposite direction (i.e., those dialysis patients with a higher serum creatinine live longer). This is contrary to the notion that well-dialyzed dialysis patients with higher Kt/V should have lower serum creatinine concentrations compared to those in whom dialysis treatment is not adequate. Lowrie and Lew (*Lowrie EG, Lew NL, 1990*), found that serum creatinine level was inversely correlated with risk for death.

Avram et al (1996) found that the enrollment serum creatinine was significantly higher among long- and very long-term hemodialysis and peritoneal survivors. In the study by Tattersall, Greenwood, and Farrington (*Tattersall J; et al, 1995*) there was no significant change in the predialysis serum creatinine values for hemodialysis patients from the time they initiated dialysis with their values 6 months later.

These results suggest that the factors that link lower predialysis serum creatinine values to increased mortality in dialysis patients may be determined when the patients commence renal replacement therapy. In the 1992 USRDS Annual Report, the investigators analyzed hemodialysis

patients initiating dialysis in 1986 and 1987 and found that increasing serum creatinine level was associated with decreasing mortality.

Fink et al (1999) studied 5388 incident hemodialysis patients followed up for almost two years and found that serum creatinine level was inversely correlated with mortality risk. Among studies of peritoneal dialysis patients, retrospective study of a cohort of 190 peritoneal patients with an average follow-up of twelve months and based on the Cox model found that a low serum creatinine was an independent variable significantly associated with increased risk of death.

B. Excess parathyroid hormone (PTH)

Excess parathyroid hormone (PTH) has long been considered detrimental to the health of patients, including those with ESRD. PTH has been implicated as a multisystem uremic toxin, and hyperparathyroidism can be a debilitating complication in dialysis patients. Hyperphosphatemia that is closely related to hyperparathyroidism is associated with increased mortality in dialysis patients.

Avram et al (2001) studied prospectively the relationship between the enrollment serum PTH and all-cause mortality in 345 hemodialysis and 277 peritoneal dialysis patients for 14 years and found that lower than expected levels of PTH in uremic patients are associated with increased mortality.

Moreover, **Guh et al (2002)** reported similar findings that low levels of serum PTH at entry and lower time-dependent PTH levels predict mortality in hemodialysis patients. **Avram et al (2001)** hypothesized that inadequate protein intake, phosphorus intake or both result in impaired development of the expected secondary hyperparathyroidism and in the excess mortality

risk inherent with malnutrition. However, to date epidemiologic studies have shown a positive association between a high serum phosphorus and poor outcome among ESRD patients. Hence, the association between serum PTH and outcome in dialysis patients may be unrelated to serum phosphorus and may reflect other aspects of nutritional status (*Avram MM; et al, 2001*).

C.Serum ferritin

Another example is serum ferritin and its association with anemia. In the general population, a low serum ferritin is a marker of iron deficiency and anemia that may not respond to erythropoietin unless iron is repleted. However, in ESRD patients, a high and not a low serum ferritin is associated with a more severe and refractory anemia. This may be due to hyporesponsiveness to erythropoietin, which can occur in the setting of the Malnutrition-Inflammation Complex Syndrome (MICS) in dialysis patients especially since ferritin is an acute phase reactant (*Kalantar-Zadeh K; et al, 2001*).