

Reverse epidemiology: paradoxical observations in haemodialysis patients

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ABSTRACT

Traditional risk factors, such as high blood pressure (BP), obesity and hypercholesterolaemia, play an important role in the development of cardiovascular disease (CVD), not only in the general population but also in patients with chronic renal disease. In recent years, it has become less clear whether these conventional risk factors are responsible for the extremely high risk of CVD in chronic haemodialysis (CHD) patients. Recent studies have shown that low BP, body mass index (BMI) and serum cholesterol are often correlated with an unfavourable clinical outcome. Thus, whereas traditional risk factors of CVD are correlated with an unfavourable outcome in the general population and patients with chronic renal failure not yet on dialysis, in CHD patients these factors appear to be protective and associated with an improved survival. Therefore, these phenomena have been referred to as 'paradoxical or reverse epidemiology'. The aetiology of this inverse relationship is not clear. Interestingly, in CHD patients, both C-reactive protein, a marker of inflammation, and (pre)albumin, a marker of nutrition, are important independent predictors of mortality. It has been speculated that what is known as the malnutrition-inflammation-atherosclerosis complex underlies, at least partly, the phenomenon of reverse epidemiology, since malnutrition causes a low BMI and hypocholesterolaemia. Hence, besides care for adequate nutrition, attempts should be made to reduce inflammation. In this respect, various haemodialysis-related factors, such as the purity of the dialysate and several characteristics of the dialyser, deserve attention.

KEYWORDS

Cardiovascular disease, chronic renal failure, haemodialysis, reverse epidemiology

INTRODUCTION

In the prosperous Western world, high blood pressure (BP), obesity and hypercholesterolaemia are established risk factors for the development of cardiovascular diseases (CVD) and cerebrovascular events.¹ Recently, chronic renal failure (CRF) has been recognised as an independent risk factor as well.² 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 haemodialysis patients, haemodialysis treatment itself might contribute to the development of CVD.³ 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.⁴ 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.^{5,6} 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'. In these patients, important independent predictors of mortality appeared to be both C-reactive protein (CRP), a marker of inflammation, and (pre)albumin, a marker of nutrition. Hence, it is conceivable that malnutrition and inflammation are related to reverse epidemiology in this respect.

BLOOD PRESSURE

Depending on the criteria used, approximately 25% of the Western population suffer from a high blood pressure.⁷ In this respect, both high systolic BP (SBP) and diastolic BP (DBP) are established risk factors for the development of CVD. Apart from CVD, both high SBP and DBP have been found to be independent predictors of the development of CRF.⁸ According to the latter study, in patients with severe hypertension the risk of CVD was tenfold over a period of 17 years. Conversely, high BP is a common complication of CRF, which contributes noticeably to the high morbidity and mortality in this patient group. As expected, in patients starting haemodialysis, the presence of hypertension appeared to be a risk factor for CVD in the long term.⁹ In these patients the relative risk (RR) of mortality was 2.2 compared with patients with a normal BP. Comparable findings have been obtained by others.¹⁰

Until recently, it seemed reasonable to assume that, once started on dialysis, CHD patients have a similar risk profile to nonuraemic persons and individuals with CRF not yet on dialysis. Recent data, however, have challenged this view. In an analysis on 649 CHD patients, Salem *et al.* found that mortality in individuals with a mean arterial pressure >114 mmHg was 27% lower than in normotensives.¹¹ The difference persisted after correction for race, diabetes, serum albumin and age. In a retrospective survey on 5433 CHD patients, CVD appeared to be increased in patients with SBP <110 mmHg or >180 mmHg.¹² Differences were not observed in the range 111 to 179 mmHg, which is surprising as persons with a high-risk profile without renal disease, such as diabetics with hypertension, do benefit from intensive BP reduction in

this range. Comparable findings were reported by Port *et al.*¹³ In an analysis of 4500 CHD patients these investigators found that low SBP (<110 mmHg) was associated with a RR for mortality of 1.86. Moreover, in this study no correlation whatsoever could be demonstrated between an elevated BP and mortality. In a recent study Takeda *et al.* also failed to show an association between hypertension and mortality.¹⁴ Altogether, these data suggest that hypertension in the predialysis phase is correlated with an increased risk of CVD, whereas in CHD patients hypotension is associated with a relatively high risk. Considering the large proportion of patients with LVH at the start of haemodialysis and the chronic fluid overload in these persons, it is conceivable that the aetiology of the BP 'risk paradox' results, at least partly, from the development of cardiac failure during long-term haemodialysis.¹³ In addition, hypotension can also be due to autonomic neuropathy, which is a common complication of severe uraemia.

BODY MASS INDEX

Just as BP and cholesterol, obesity is an established independent risk factor of CVD in the general population. Recently, 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 kg/m²).¹⁵ In 1982 Degoulet *et al.* reported for the first time that underweight was associated with an increased mortality in CHD patients.¹⁶ Conversely, in a historical prospective study on 1346 CHD patients, BMI > 27.5 kg/m² was correlated with the highest survival, if compared with low (<20 kg/m²) and normal (20 to 27.5 kg/m²) BMI values.¹⁷ 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.¹⁸ 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.¹⁹ 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.* studied 116 Japanese CHD patients who were followed for 12 years.²⁰ According to these investigators 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.²¹ In an attempt to understand the BMI risk paradox, Fleischman *et al.* studied the relation between several parameters of nutrition, including prealbumin and lipids, and BP.²² From this study it appeared that prealbumin, which is a sensitive biochemical marker for the state of nutrition, was positively correlated with

both total cholesterol and BMI. These findings support the view that high BMI and high serum cholesterol both result from an adequate nutrition in CHD patients.

Interestingly, in these patients (pre)albumin appeared to be one of the strongest predictors of survival.²³

Despite the above-mentioned considerations, the cause of the improved survival in obese CHD patients remains obscure. Adipose tissue is an important producer of various hormones, growth factors and cytokines, such as the proinflammatory cytokine tumour necrosis factor α , angiotensin II (AII) and leptin.²⁴ An increased local production of AII contributes to insulin resistance and the metabolic syndrome.²⁵ Leptin suppresses food intake by inhibiting neuropeptide Y and promotes the proliferate effects of AII. Therefore, it is conceivable that the balance between the negative effects of adipose tissue and the advantageous influence of an adequate nutritional state is, at least in the short term, in favour of the latter.²³

SERUM CHOLESTEROL

Uraemic and nonuraemic individuals share a number of conventional risk factors of CVD, such as old age, comorbidity and smoking. However, as outlined before, the presence of other traditional risk factors, such as hypertension and obesity, is correlated with a lower risk of CVD in CHD patients. These paradoxical observations are possibly explained by the fact that high BMI results from sufficient nutrition, which is associated with a lower mortality risk in this patient group. What about the interrelationship between BMI and cholesterol in these patients? Is low serum cholesterol also correlated with reduced survival, and should cholesterol, being a traditional risk factor of CVD in the general population,²⁶ be considered a reverse risk factor in CHD patients? Indeed, as described by Iseki *et al.*, low cholesterol appeared to be an independent predictor of mortality in a cohort of 1176 CHD patients who were followed for a period of ten years.⁶ Moreover, serum cholesterol was positively correlated with serum albumin and negatively with CRP. According to the authors, these findings support the view that low albumin and cholesterol values are manifestations of an inadequate state of nutrition, resulting from chronic inflammation. Indeed, several authors have reported on a striking correlation between inflammation, as measured by CRP, and malnutrition, as measured by (pre)albumin and/or serum cholesterol concentrations.²⁷ Interestingly, in apparently healthy persons, CRP appeared to be more predictive of CVD than LDL cholesterol.²⁸ For completeness, it should be mentioned that in predialysis patients non-HDL-C was unquestionably correlated with CVD.²⁹ Thus, whereas cholesterol is one of the traditional risk factors for CVD in renal patients not yet on dialysis,

reverse epidemiology is observed in CHD patients. Recently, Kalantar-Zadeh *et al.* estimated the relative risk of mortality in a hypothetical model that was based on the state of nutrition and serum cholesterol levels.³⁰ From their calculations it appeared that the short-term risk of mortality is influenced predominantly by hypocholesterolaemia in underweight patients, whereas the risk over a longer period of time is mainly influenced by high serum cholesterol levels in well-nourished patients. Combination of these models indicated that the short-term model, showing a survival disadvantage of undernutrition in a shorter period of time, overwhelms the long-term negative effects of overnutrition on mortality.

Homocysteine

Recently, total plasma homocysteine (tHcy) appeared to be an independent risk factor of CVD, both in the general population³¹ and in patients with CRF.³² Hcy is a sulph-hydril-amino acid resulting from the demethylation of the essential amino acid methionine. Hyperhomocysteinaemia (hyperHcy) may contribute to atherosclerosis by promoting oxidative stress and preventing endothelial relaxation. In physiological conditions, several enzymes and co-factors are involved in the degradation of Hcy, including vitamin B6, vitamin B12 and folic acid. In CRF, however, the metabolism of Hcy is disturbed. HyperHcy is found in >90% of dialysis patients. Although a decrease in the plasma concentrations of tHcy has been observed after the administration of vitamins, and haemodialysis with superflux devices,³³ normalisation in these patients is rare. Moreover, as of yet, no studies have been published showing that a long-lasting decline of tHcy is associated with a decrease in the atherosclerotic process. In a study of 1919 CHD patients, Kalar-Zadeh *et al.*³⁴ showed that low tHcy values were correlated with a high incidence of hospitalisations and mortality. Moreover, tHcy was positively associated with markers of nutrition and muscle mass, such as (pre)albumin and creatinine. In fact, these findings are not surprising, as circulating Hcy is largely bound to serum albumin. Thus, whereas tHcy has recently been recognised as a risk factor for CVD in the general population, paradoxical observations are found in CHD patients. Comparable findings were published by others,³⁵ whereas in an Italian survey of 175 CHD patients, high plasma tHcy values were associated with an increased incidence in CVD.³⁶

Advanced glycation end products

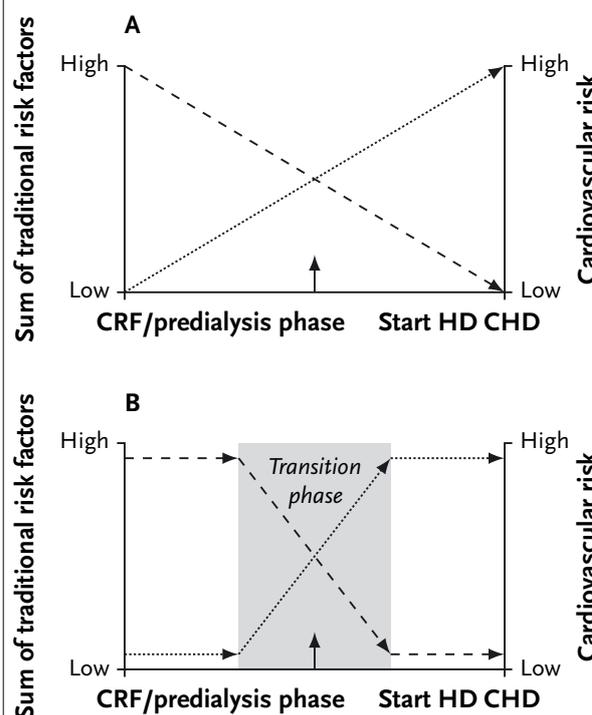
Advanced glycation end products (AGEs) result from nonenzymatic reactions between reducing sugars and amino groups on proteins. As these substances are relatively resistant to enzymatic degradation, peptide-bound degradation products are formed, which are known as AGE peptides. The latter substances are biologically active

and may damage or alter the structure and function of various biological systems, including long-lived collagen. Increased concentrations of serum AGEs are found in elderly people, diabetics and patients with CRF. Besides increased serum concentrations, AGEs have been demonstrated in coronary atheroma and heart muscle tissue in patients with CVD,³⁷ and in brain tissue in patients with Alzheimer's disease.³⁸ In CHD patients AGEs contribute to uraemic toxicity and are involved in the development of the carpal tunnel syndrome, dialysis-related amyloidosis and peripheral polyneuropathy.³⁹ Although we have recently shown that AGE peptides can be lowered in the long term by haemodialysis with superflux dialysers,⁴⁰ it is unknown whether permanent reduction is beneficial to patients. In a cross-sectional study, Schwedler *et al.* analysed the predictive power of serum AGEs and CRP on total mortality.⁴¹ Unexpectedly, the highest survival rates were found in individuals with high serum AGE-peptide levels and low CRP. As AGEs are abundantly present in food (AGEs are formed during the heating of food and are the source of the aroma and brown colour),⁴² the authors suggested that high serum AGE levels reflect an adequate nutritional state.

DISCUSSION

Several traditional risk factors of CVD in the general population, such as hypertension, obesity and hypercholesterolaemia, are predictive of CVD in patients with CRF not yet on dialysis, whereas the reverse is observed in CHD patients. In these individuals, low BP, underweight and low serum cholesterol levels appear to be independent risk factors of CVD, whereas high blood concentrations of Hcy and AGEs seem protective. Interestingly, reversal back to traditional epidemiology has been described after successful renal transplantation.⁴³ How should we deal with these apparently contradictory observations? Should we dissuade our CHD patients from losing weight if they are obese, or advise them to eat plenty of saturated fats if they have a low serum cholesterol? Although solid data on this subject are lacking, some restraint may be justified. As mentioned, not only BP, but also BMI and cholesterol are established risk factors in the predialysis phase, whereas an almost complete reversal is observed during the dialysis period. Whether this reversal is gradual or more or less abrupt within some kind of transition phase is currently a matter of speculation (*figure 1*). The aetiology of the switch to the opposite direction in CHD patients is not clear. It is possible that the epidemiology in CHD patients is reversed due to survival bias. As outlined before, patients with CRF who are not yet on dialysis have a high mortality and only a small number of these patients reach end-stage renal disease. Therefore, it is

Figure 1 Two hypothetical models representing the switch in cardiovascular risk based on traditional risk factors leading to reverse epidemiology



A: gradually developing reverse epidemiology. B: more or less defined transition phase in the development of reverse epidemiology. For clarification see text. CRF = chronic renal failure; (C)HD = (chronic) haemodialysis.

conceivable that selection of survivors leads to a different epidemiology. In a longitudinal follow-up study of the natural history of CRF, Keith *et al.* showed that the prevalence of hypertension and hyperlipidaemia was indeed lower in patients with CRF who died before advancing to end-stage renal disease or renal replacement therapy than in survivors.⁴⁴ In this study approximately 28,000 patients in the USA who had an estimated glomerular filtration rate of less than 90 ml/min per 1.73 m² were observed for up to 66 months after enrolment or until renal replacement therapy, death or disenrolment from the health plan. In *table 1* the prevalence of hypertension and hyperlipidaemia at baseline is shown in the different stages of chronic renal failure according to the Kidney Disease Outcomes Quality Initiatives (K/DOQI) guidelines; the prevalence of hyperlipidaemia and hypertension in CHD is also added.^{45,46} As discussed before, underweight, as indicated by low BMI, and low blood levels of cholesterol, Hcy and AGEs may result from malnourishment. Interestingly, in CHD patients, both CRP, a marker of inflammation, and (pre)albumin, a marker of nutrition, are important independent predictors of mortality. These

Table 1 Prevalence of hypertension and hyperlipidaemia in patients with chronic kidney disease undergoing chronic haemodialysis

	Prevalence (%)	
	Hyperlipidaemia	Hypertension
GFR 60-89, no proteinuria (n=14191)*	1874 (13.2)	4182 (29.5)
Stage 2 (n=1723)*	236 (13.7)	609 (35.3)
Stage 3 (n=11134)*	1556 (14.0)	5189 (46.6)
Stage 4 (n=622)*	86 (13.8)	322 (51.8)
Chronic haemodialysis	(34)**	(86)***

GFR = glomerular filtration rates; estimated in millilitres per minute per 1.73 m². Staging of chronic kidney disease according to the K/DOQI guidelines. *Data adopted from reference 4. **Data adopted from reference 45. Hyperlipidaemia defined as a total cholesterol >200mg/dl. ***Data adopted from reference 46. Hypertension is defined as a predialysis blood pressure >150/85 mmHg.

two conditions are brought together in what is known as malnutrition-inflammation-atherosclerosis (MIA) complex, indicating the important association between malnutrition inflammation and atherosclerotic cardiovascular disease, which may cause a high early mortality. Traditional risk factors such as hypercholesterolaemia, high BMI and hyperHcy are associated with a limited long-term survival in the general population. In renal patients, however, these factors are related to an improved short-term survival as they represent a state of adequate nutrition. Therefore, it has been speculated that, apart from survival bias, the MIA complex underlies the phenomenon of 'reverse epidemiology'.⁴⁷ If this is the case, reverse epidemiology may be reversed back to traditional epidemiology once the MIA complex is treated. Hence, besides care for adequate nutrition, attempts to reduce inflammation may also be advisable. In this respect, various haemodialysis-related factors, such as the purity of the dialysate and several characteristics of the dialyser, deserve attention.³ Whether the anti-inflammatory properties of HMG-CoA reductase inhibitors⁴⁸ and angiotensin-converting enzyme inhibitors⁴⁹ contribute to an improved clinical outcome is currently unclear. Although treatment with simvastatin⁵⁰ and atorvastatin⁵¹ has lowered both serum cholesterol and CRP levels in CHD patients, a recent prospective trial comparing atorvastatin with placebo failed to show any difference in the clinical outcome between the treatment groups.⁵² Therefore, it is possible that new standards or goals for such traditional risk factors as BP, BMI and serum cholesterol should be considered in long-term haemodialysis patients.

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