INTRODUCTION

In dialysis patients, cardiovascular disease is the predominant cause of mortality ***(Brunner and Selwood, 1992)***. An increased risk of cardiovascular morbidity and mortality is also seen in earlier stages of chronic kidney disease. Traditional cardiovascular risk factors are common in these patients, but alone, they may not be sufficient to account for the high prevalence of cardiovascular disease in this population. Recent clinical evidence demonstrates that chronic inflammation, a non-traditional risk factor, which is commonly observed in end-stage renal disease patients, may be associated with atherosclerotic cardiovascular disease and anemia in patients with end-stage renal disease ***(USRDS, 1999)***.

Chronic inflammation characterized by increased C reactive protein levels, strongly predict cardiovascular disease in both renal and non-renal patients. Both anemia and biocompatibility of hemodialysis result in chronic inflammatory syndrome. Renal dysfunction may directly cause an increase in inflammatory mediators via a

mechanism of increasing oxidative stress ***(Zoccali et al., 2001)***.

Chronic kidney disease can be viewed as a clinical model of mild protracted systemic inflammation that is intrinsically associated with oxidative stress, endothelial dysfunction and hemostatic activation, which are all important mediators of atherosclerosis and thrombotic events ***(Ross, 1999)***.

Iervasi et al. found that low T3 syndrome is a tsrong predictor of death in patients with heart disease in the general population ***(Stinvenkel et al., 2002)***.

Because inflammation influences thyroid function, it was hypothesized that low plasma free triiodothyronine in end-stage renal disease may be an unsuspected expression of the inflammatory state of these patients, and could be a non-traditional cardiovascular risk factor ***(Zoccali, 2003)***.

AIM OF THE WORK

To detect the relation between low free triiodothyronine (FT3) and inflammatory state in chronic renal failure patients undergoing regular hemodialysis, as well as its relation to cardiovascular disease in these patients.

Chapter (1)

CARDIOVASCULAR RISK FACTORS IN END STAGE RENAL DISEASE

Cardiovascular disease causes more than 50% of deaths among maintenance dialysis patients, followed by infection (approximately 15%) ***(Brunner and Selwood, 1992 and USRDS, 1999)***.

In the last three decades intensive investigations have lead to a paradigm shift in the interpretation of atherosclerosis, from a purely metabolic process, mainly driven by hypercholesterolemia, to a disease where inflammation is the dominant alteration. This paradigm shift owes very much to the late response to injury theory of atherosclerosis ***(Zoccali et al., 2001)***.

The response to injury theory holds that offending factors damage the endothelium and disrupt its physiologic properties. The adhesiveness of the endothelium to leukocytes and platelets is increased and the endothelium synthesizes vasoactive molecules, cytokines, and growth factors. Macrophages migrate in the arterial wall where

they take up cholesterol and lipids and become foam cells ***(Ross, 1999)***.

The lipid core is thus generated. A fibrous cap covers the lipid core and the plaque alters the hemodynamic properties of vessel. Plaques may ulcer thus triggering thrombosis. Thrombi detach from the ulcerated plaque and eventually occlude arterial vessels at distant districts, the heart and the brain, thus causing the most feared consequences of atherosclerosis ***(Zoccali et al., 2001)***.

In patients with ESRD systemic evidence of a micro-inflammatory process is associated with atherosclerosis as there is direct relationship between atherosclerotic plaques and C reactive protein (CRP). More importantly in these patients serum CRP represents a strong predictor of adverse cardiovascular events. In a German cohort of dialysis patients the cardiovascular death rate was about 5 times higher in, patients in the 4th CRP quartile than in those in the first CRP quartile and these results were fully confirmed also in an American study by Kaysen group ***(Stinvenkel et al., 2002)***.

Dialysis treatment has long been suspected as a culprit of inflammation in ESRD. It has been shown that IL-6, an inflammation marker increases by the 68% two hours after dialysis clearly showing that dialysis per se is an inflammatory stimulus. However, IL-6 in baseline conditions was 20 times higher than in healthy individuals indicating that the increase induced by dialysis is just a tiny fraction of the problem. Furthermore evidence of inflammation as measured by serum CRP is evident in about 1/3 of patients before dialysis. Overall it is reasonable to say that factors other than dialysis treatment are implicated in inflammation in ESRD ***(Zoccali, 2003)***.

Angiotensin II is a recognized pro-inflammatory substance and growth promoter. Double transgenic rats overexpressing the angiotensinogen and renin gene display marked left ventricular hypertrophy and the texture of the myocardium in these rats shows an important infiltration of macrophages, that is inflammatory changes. A similar process may be at work in ESRD disease because it has been shown that left ventricular mass in these patients is directly related to plasma rennin activity (PRA). The higher

the PRA the higher the left ventricular mass ***(Zoccali et al., 2001)***.

The sympathetic system is a major regulator of cardiovascular function but has also many other important functions. It interferes with immune mechanism and inflammation and norepinephrine (NE) is a growth promoter of myocardial cells. NE and sympathetic fibers are well represented in lymph nodes and the sympathetic system is recognized as a modulator of the systemic response to inflammation ***(Zoccali et al., 2002)***.

That inflammatory mechanism may be modulated by the sympathetic system in heart diseases is suggested by the fact that treatment with betab. Lockers reduces the high level of TNF alpha in patients with dilated cardiomyopathy. On the other hand norepinephrine is a recognized growth promoter for myocardial cells and in experimental animals it induces LVH by mechanisms independent of BP. In this regard it is interesting noting that in patients with ESRD circulating norepinephrine is directly related to the muscular component of the LV, the mean ventricular wall, as well as with the prevalence of concentric hypertrophy. More importantly, raised NE is a

predictor of cardio-vascular death. Of note both these effects on the heart and on survival are independent of arterial pressure ***(Zoccali et al., 2002)***.

Chronic volume overload besides being a hypertension trigger also induces the expression of pro inflammatory, molecules in the heart. Indeed in an experimental model of volume overload, Monocyte Chemoattractant Protein (MCP) is overexpressed in cardiomyocytes and there is evidence that in other experiments that also TNF and IL6 are over expressed in myocardial cells when end diastolic pressure is high. It is interesting that the overexpression of MCP occurs not only in animals with decompensated heart failure but also in those that have compensated forms of the disease.

Fibrinogen is an acute phase reactant of particular interest in relation to volume overload, indeed it is not only responsive to inflammatory stimuli like IL-6 but also to volume stimuli ***(Behr et al., 2002)***.

Indeed in heart disease patients without systemic evidence of inflammation that also display raised plasma volume the synthesis rate and the plasma concentration of

fibrinogen is increased. In support of a volume expansion as a potential trigger of fibrinogen synthesis Kaysen has recently shown that the plasma concentration of this protein is directly related to albumin synthesis. Because the plasma concentration of fibrinogen reflects two powerful cardiovascular event triggers (volume overload and inflammation) it is expected to be strongly related to cardiovascular events. In keeping with this hypothesis fibrinogen is indeed a strong predictor of incident cardiovascular events in patients with ESRD ***(Kaysen et al., 2003)***.

Cigarette smoke is a deadly gas mixture. Smoking is a strong oxidant stimulus and has an inflammatory effect. Indeed macrophages of asymptomatic smokers produce a greater amount of inflammatory cytokines than those of healthy age and sex matched controls ***(Zoccali et al., 2001)***.

Diabetics with ESRD are at extreme risk of cardiovascular events. The very high risk of diabetes is very often associated with other risk factors, hypercholes-terolemia and hypertension. Furthermore diabetics on dialysis have a long history of insulin resistance and the exposure to advanced glycation endproducts in these

patients is much higher than that of other heart disease patients. It is well recognized that advanced glycation end-products constitute an inflammatory stimulus and insulin resistance has been linked with raised CRP in the general population ***(Zoccali et al., 2001)***.

Vascular calcifications in the coronary, in heart valves and in peripheral arteries are pervasive in ESRD. Undoubtedly uncontrolled hyperphosphatemia favours vascular calcifications because the risk of all cause mortality is 21 % higher and that of incident cardiovascular events 45% higher in patients with serum P >6.5 mgldl. However hyperphosphatemia and hypercalcemia is just one face of the coin ***(Wang et al., 2003)***. Osteoclast-like cells are demonstrable in heart valves and in arterial vessels. Their ability to affect phosphate metabolism is documented by their alkaline phosphatase activity. It is interesting to note that this activity is much enhanced when these cells are co-cultured with monocyte macrophages thus providing a link between inflammation and vascular calcification ***(Tintut et al., 2002)***. On the other hand in heart valves and arterial vessels as well there is a true process of ossification. When we have true lamellar bone, inhibitors

of calcification are important, particularly so in patients with ESRD. In this regard Fetuin is a most interesting calcification inhibitor and inverse acute phase reactant. When Fetuin is low, inflammation and calcification should be more likely ***(Ketteler et al., 2002)***. In agreement with this hypothesis, Ketteler has recently shown that CV events free survival is shorter in patients with low Fetuin than in those with relatively higher values ***(Ketteler et al., 2002)***.

Evidence has been recently provided that Homo-cysteine constitutes an important inflammatory stimulus. Hyperhomocysteinemia was associated with high cardio-vascular morbidity in two cohort studies in dialysis patients ***(Moustapha et al., 1998 and Mallamaci et al., 2002)***.

Infections particularly, Chlamydia Pneumoniae have been implicated as potential triggers of atherosclerotic complications in patients with chronic renal disease. However, the association between anti-Chlamydia antibodies and incident cardiovascular events seems to depend on the confounding effect of some traditional risk factors ***(Zoccali et al., 2003)***.

Under normal conditions nitric oxide (NO) is continuously generated in the endothelium because the enzyme NO synthase transforms L Arginine into NO and citrulline. NO in the endothelium has a protective role for the cardiovascular system because NO inhibits vascular muscle cells proliferation, platelets aggregability and the adhesion of monocytes to the endothelium, all processes that trigger atherosclerosis. There are endogenous inhibitors of this enzyme of which asymmetric dimethylarginine (ADMA) is the most important. ADMA can be eliminated by the kidney but there is a very important alternative metabolic route that is cellular metabolism by Diethyl DiaminoHydrolase an enzyme present within the endothelial cells which is very sensitive to oxidative stress ***(Cooke, 2000)***. Oxidative stress is prevalent in ESRD ***(Himmelfarb et al., 2002)***. Therefore, high ADMA in this condition may be an expression of the high rate of generation of oxidants. ADMA per se seems responsible for 52% higher risk of death and for 34% higher risk of cardiovascular events in hemodialysis patients ***(Zoccali et al., 2001)***. Besides predicting cardiovascular events, high ADMA is strongly associated with well established risk markers as intima-media

thickness, in the carotid arteries ***(Zoccali et al., 2002)*** and concentric left ventricular hyper-trophy ***(Zoccali et al., 2002)***.

ADMA is a potentially modifiable risk factor. Treatments aimed at reducing oxidative stress or high doses of the NO precursor L-arginine constitute interesting opportunities for intervention on this putative risk factor. Perhaps further information on the role of ADMA in cardiovascular complications in ESRD will be available from trials aimed at reducing hypercholesterolemia, inflammation, and oxidative stress in hemodialysis patients ***(Wanner et al., 1999)***.

Chapter (2)

THYROID HORMONE DYSFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Thyroid Hormone Abnormalities in ESRD:

Patients with ESRD have multiple alterations of thyroid hormone metabolism in the absence of concurrent thyroid disease. These may include elevated basal TSH values, which may transiently increase to greater than 10 mU/liter, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rates. In addition, serum total and free T3 and T4 values may be reduced, free rT3 levels are elevated while total values are normal, serum binding protein concentrations may be altered and disease-specific inhibitors reduce serum T4 binding. Changes in T4 and T3 transfer, distribution, and metabolism resemble those of other non-thyroidal illnesses, while changes in rT3 metabolism are disease specific. Dialysis therapy minimally affects thyroid hormone metabolism, while zinc and erythropoietin administration may partially reverse thyroid hormone abnormalities. Thyroid hormone

metabolism normalizes with renal transplantation; however, glucocorticoid therapy may induce additional changes ***(Kaptein, 1996)***.

Thyroid Neoplasia in ESRD:

ESRD patients may have an increased frequency of goiter, thyroid nodules, thyroid carcinoma, and hypothyroidism. Goiter and hypothyroidism may be induced by iodide excess, due to reduced renal iodide excretion, and may be reversed with iodide restriction in some patients. The increased frequency of thyroid nodules and malignancies in ESRD may relate to secondary hyperparathyroidism. After renal transplantation, the higher frequency of thyroid malignancies may relate to the immunosuppressed state. Clinical symptoms and signs and biochemical features of hypothyroidism and hyper-thyroidism may be altered by concurrent ESRD. ESRD patients with hyperthyroidism or follicular neoplasms require reduced dosages of Na ^{131}I depending upon type, frequency, and duration of dialysis therapy ***(Kaptein, 1996)***.