TLR-4 AS A CONTRIBUTOR TO ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN END-STAGE RENAL DISEASE.

Thesis
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INTRODUCTION

Atherosclerosis is a multi-factorial inflammatory disease and is the primary initiator of coronary artery and cerebrovascular disease. Initially believed to be exclusively lipid-driven, recent evidence demonstrates that inflammation is a significant driving force of the disease ***(Seneviratne et al., 2011)***. It has been shown that circulating immune cells, including monocytes, that attach to inflamed vessels by interacting with adhesion molecules and chemokines secreted by the activated endothelium play a pivotal role in atherogenesis ***(Hansson, 2005).*** Subsequently, secreted cytokines can activate residing macrophages, endothelial cells and vascular smooth muscle cells, which actively participate in cellular immunity and contribute to local inflammation ***(Libby, 2002).***

The family of Toll-like receptors (TLRs) initiates an innate immune response after recognition of pathogen-associated molecular patterns (PAMPs) ***(Pasterkamp et al., 2004).*** Both immune and non-immune cells express inflammatory cytokines and chemokines upon stimulation of

the TLR with their specific ligands. Not only exogenous ligands but also endogenous ligands that are expressed during arterial injury are recognized by TLR4. Evidence is accumulating that TLRs, and particularly TLR4, are important players in the initiation and progression of atherosclerotic disease. Its activation stimulates mononuclear phagocytosis to secrete chemokines that are involved in the recruitment of monocytes and T-lymphocytes to the arterial wall ***(Reape et al., 1999).***

Atherosclerosis is common in patients with chronic kidney disease (CKD), and cardiovascular disease (CVD) represents a major cause of death in these patients, especially, in patients with end-stage renal disease(ESRD) ***(Koike and Nitta, 2011).*** Although traditional risk factors, such as diabetes mellitus, hypertension, dyslipidemia and advanced age, are prevalent in ESRD patients they may not be sufficient by themselves to account for the high prevalence of CVD in patients with this condition. Thus, the search for other, non-traditional, risk factors that may be involved in the pathogenesis of uremic CVD has been an area of intense study. Data suggest that the accelerated atherosclerotic process of ESRD may involve several interrelated processes, such as

oxidative stress, endothelial dysfunction and vascular calcification, in a milieu of constant low-grade inflammation. Available data suggest that pro-inflammatory cytokines play a central role in the genesis of both malnutrition and CVD in ESRD ***(Yao et al., 2004).***

AIM OF THE WORk

The purpose of this study is to assess the expression of TLR 4+ monocytes in peripheral blood in patients with chronic kidney disease stage V on maintenance hemodialysis with and without cardiovascular events and to explore the correlation between circulating TLR-4+ monocytes and traditional CV risk factors.

Chronic kidney Disease

CKD is increasingly recognized as a public health problem and is usually characterised by an asymptomatic period, which is potentially detectable. Chronic kidney disease (CKD) refers to the many clinical abnormalities that progressively worse as kidney function declines. CKD results from a large number of systemic diseases that damage the kidney or from disorders that are intrinsic to the kidney ***(Russell et al., 2001).***

In CKD, the damage is rarely repaired, so loss of function persists. This distinguishes CKD from acute kidney damage, which can be repaired to permit the return of kidney function. The chronic loss of kidney function generates even more kidney damage and more severe clinical abnormalities. As a result, CKD progressively worsens even if the disorder that caused it becomes inactive. When the kidney fails to perform most of its functions, the clinical state is called end-stage renal disease (ESRD), and dialysis or transplantation is required to sustain life ***(Russell et al., 2001).***

Numbers of prevalent CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. Individuals aged 75 years and older have experienced the greatest increase in incidence (98% over the last decade), attributable in part to improved survival of individuals with cardiovascular disease and diabetes mellitus and expanded access to renal replacement therapy for older patients ***(Russell et al., 2001).***

Definition of chronic kidney disease:

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease (2004) recommend that CKD be adopted to define the presence of kidney injury and impaired kidney function .

The National Kidney Foundation definition at 2004 includes the presence for 3 or more months of impaired renal function across a continuum of renal injury from isolated anatomic, radiographic, biomarker,and urinary abnormalities to decreased glomerular filtration rate(GFR), irrespective of the primary cause of therenal injury. Classification of CKD requires that the clinician establish the presence or absence of

renal injury, estimate the GFR, and then determine that kidney disease has persisted for 3 or more months.

An estimated GFR above 60 mL/min/1.73 m2, in the absence of other anatomic, radiographic, or urinary abnormalities, is not classified as CKD. The ***National Kidney Foundation classification*** defines five stages of CKD by increasing degree of impaired kidney function . As kidney damage progresses the remaining nephrons compensate for the reduction in nephron mass by increasing the single nephron filtration rate, and this hyper filtration promotes further injury ***(Brenner and Mackenzie, 1997).***

At each stage patients can benefit from measures that delay or prevent the progressive loss of renal function, modification of medications with renal clearance, avoidance of nephrotoxins, and reduction of cardiovascular risk factors **(*Peter et al., 2003).***

Patients with CKD need to be monitored for progression of kidney failure, and patients who advance to CKD stage 3 require increased attention to control of hypertension, anemia, renal bone disease, and nutrition. Recognition and early referral of patients who advance to stage 4 and 5 CKD is important if the transition to ESRD treatment is to be

successful. There is evidence that patients in these stages of CKD may not be recognized and appropriately manage stage 4 and 5 CKD before the onset of ESRD. For example, delayed referral for ESRD treatment has been associated with less than optimal vascular access placement; failure to manage renal bone disease and nutrition; poor anemia control; impaired quality of life; and increased risk of severe hypertension, uremic symptoms, pulmonary edema, and emergent dialysis ***(Roubicek et al.,2002).***

Classification Of CKD :

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) at 2004 stratified chronic kidney disease into five stages according to glomerular filtration rate and the presence of kidney damage:

- Stage 1: GFR >90 ml/min/1.73 m2 with other evidence of kidney damage (persistent microalbuminuria, persistent proteinuria, persistent haematuria, structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, or biopsy-proven chronic glomerulonephritis) .
  Stage 2: GFR 60–89 ml/min/1.73 m2 with other

evidence of kidney damage . Stage 3: GFR 30–59 ml/min/1.73 m2.

- Stage 4: GFR 15–29 ml/min/1.73 m2.
- Stage 5: GFR <15 ml/min/1.73 m2.

Epidemiology :

The incidence and prevalence of kidney disease worldwide and in the United States has risen markedly in the past decade ***(Eknoyan et al.,2001).***

About 20 million Americans from 1988 to 1994—or approximately 11% of all US adults—are living with CKD(stages 1–5), and the incidence and prevalence of kidney disease are increasing] ***(Lee ,2003).***

Epidemiologically, a major observation of the last few years has been the recognition of the very large number of people who have GFR between 30 and 59 mL/min/1.73 m2, placing them at stage 3 CKD. They represent the bulk of patients who suffer most of the consequences of CKD in the United States. While approximately 400,000 patients in the United States have stage 4 (severe) CKD and about 300,000 are on dialysis, the majority of CKD patients (7.6 million) are in stage 3 ***(Lee ,2003).***

There are a number of populations that are considered to be at high risk of developing ESRD ,Clinicians should be particularly aware of four groups of high-risk individuals likely to be encountered on a frequent basis:

1. patients with hypertension.
2. patients with diabetes mellitus.
3. patients with cardiovascular disease.
4. family members of incident ESRD patien. Members of these high-risk groups benefit from early detection and treatment of CKD and clinicians caring for them should be particularly attentive to opportunities to screen for kidney disease when caring for them***(National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease,.2002).***

Elevated blood pressure is an important modifiable risk factor for progressive CKD regardless of the initial cause of kidney injury. Observational studies have established that patients with non-malignant, none accelerated levels of hypertension are at high risk of progressive renal insufficiency ***(Haroun et al.,2003).*** Evidence from clinical trials shows that blood pressure reduction reduces the rate of loss of renal

function and progression to renal failure and this information has been incorporated into widely disseminated clinical practice guidelines (***Chobanian et al.,2003).***

These studies have demonstrated a strong and graded association between blood pressure reduction and reduction in rate of decline in GFR that persists to blood pressure levels of 130/80 mm Hg, and this threshold has been adopted for management of hypertensive patients with CKD ***(Wright et al.,2002).***

The details of gender and race specific patients reported that the risk for developing macroalbuminuria was reduced by 65% for patients treated with angiotensin-converting enzyme inhibitors and, among subjects with overt proteinuria, the risk for doubling of serum creatinine or developing ESRD was reduced by 40%, suggesting a stronger benefit for individuals treated with renin-angiotensin system blockade earlier in the course of their CKD ***(Kshirsagar AV,etal.,2002).***

Epidemiology in Our countries:

End stage renal disease in north Africa :

There are many similarities in the profile of the renal disease in the five countries of north Africa, reflecting their close resemblance in ethnic background, and socioeconomic standards. North Africa is the term commonly used to refer to five countries: Morocco, Algeria, Tunisia, Libya and Egypt with a total area of 5.8 million square kilometers, The population inhabiting this region is about 138 million ***(Barsoum RS,2002).***

The incidence of renal disease is much higher than that in the West yet the prevalence is relatively lower, which mirrors the inadequacy of medical care facilities. All five countries are classified under the "medium-economy" category by World Bank criteria, The reported annual incidence of ESRD ranges between 34 and 200 per million population (pmp), it indicates the relatively poor renal health care standards in certain North African countries. Despite the relatively high mortality, the prevalence of ESRD is increasing***(Barsoum RS,2002).***

Risk factors associated with progression of chronic kidney disease:

The early identification and treatment of CKD is essential to decrease the risk of cardiovascular disease, progression to ESRD, and mortality. Identification of high-risk groups can help clinicians monitor renal function and identify people with CKD at an earlier disease stage. Although general population screening may not be cost-effective, targeted screening directed at subgroups of the population who might derive the most benefit from CKD detection was shown to be an effective strategy ***(National Kidney Foundation ,2008).***

A national programme to identify vulnerability to vascular diseases was announced by the Health Secretary in April 2008, following initial results from modelling work carried out by the Department of Health. This work suggested that a vascular check programme would prevent 4000 people a year from developing diabetes and could also detect at least 25,000 cases of diabetes or kidney disease earlier. In those conditions where the prevalence of CKD is high and the risks of preventable complications are increased, testing for CKD is clearly warranted.

The ***KEEP programme*** identified people with diabetes and hypertension, or people with a first-line relative (parent, grandparent, brother or sister) with diabetes, high blood pressure or kidney disease as being at high risk of CKD.

The ***UK CKD guidelines*** also included those with a high risk of obstructive uropathy, all forms of CVD, multisystem diseases with the potential to involve the kidney such as SLE, and conditions requiring long-term treatment with potentially nephrotoxic drugs***(Taal ,2007).***

- **Age:**

  The association between developing CKD and age was examined in cross-sectional studies conducted in the ***UK(Drey et al.,2003) ,Norway(Hallan et al.,2006), USA(Coresh et al.,2007) and Australia(Chadban et al,2003).***

- **Gender:**

  The association between developing CKD and gender was examined in cross-sectional studies conducted in ***the UK(Drey et al.,2003),Norway(Hallan et al.,2006), USA(Coresh et al.,2003) and Australia(Chadban et al.,2003).***