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Cardiovascular Complications in Renal Diseases

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1. Introduction

Patients with chronic renal disease (CRD) represent an important segment of Tunisian population, and mostly because of the high risk of cardiovascular disease (CVD) associated with renal insufficiency, detection and treatment of chronic renal disease is now a public health priority (Abderrahim E et al., 2001, Ben Maïz H et al., 2006, Council E et al., 2008). The increased incidence of CVD is likely to be the result of a high prevalence of both traditional risk factors, such as diabetes mellitus, hypertension, dyslipidemia and smoking. Non traditional risk factors, such as hyperhomocysteinemia, oxidative stress and inflammation have been taken into account.

Homocysteine (Hcy) is an amino acid that circulates in the blood. An elevated serum concentration of homocysteine is a known risk factor for atherosclerosis and is associated with an increased risk of myocardial infarction and health. Accumulating evidence suggests that the Hcy thioester metabolite, hcy-thiolactone, has an important role in atherothrombosis. Hcy-thiolactone is a product of an error-editing reaction in protein biosynthesis, which forms when Hcy is mistakenly selected by methionyl-tRNA synthetase. The thioester chemistry of Hcy-thiolactone underlies its ability of form isopeptide bonds with protein lysines residues, which impairs or alters protein function. Protein targets for modification by Hcy-thiolactone include fibrogen, LDL, HDL, albumin, hemoglobin and ferritin. Pathophysiological consequences of protein N-homocysteinylation include protein and cell damage, activation of an adaptive immune response, synthesis of auto-antibodies against N-hcy-proteins, and enhanced thrombosis caused by N-hcy-fibrogen. The development of highly sensitive chemical and immunohistochemical assays has provided evidence for the contribution of the Hcy-thiolactone pathway to pathophysiology of the vascular system. In particular, conditions predisposing to atherosclerosis, such as genetic or dietary hyperhomocysteinemia, have been shown to lead to elevation of Hcy-thiolactone and N-hcy-protein.

Oxidative stress plays an important role in the pathogenesis of atherosclerosis and cardiovascular disease. Reactive oxygen species (ROS) production is toxic via their effects on cellular components such as denaturing proteins, membrane lipids and DNA. Oxidative

stress may be defined as an imbalance between the production and degradation of ROS such as superoxide anion, hydrogen peroxide, lipid peroxides and peroxynitrite. Enzymatic inactivation of ROS is achieved mainly by glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase. GPx, the ubiquitous intracellular form and key antioxidant enzyme within most cells, including the endothelium, uses glutathione to reduce hydrogen peroxide to water and lipid peroxides to their respective alcohols, and it also acts as a peroxynitrite reductase. In mice GPx deficiency results in abnormal vascular and cardiac function and structure. Similarly, SOD is represented by three different ubiquitously expressed enzymes that convert superoxide anion to hydrogen peroxide: cytosolic copper- and zinc-containing SOD, mitochondrial manganese-containing SOD and extracellular SOD. Extracellular SOD is most active in the vessel wall and has been shown to regulate the availability of nitric oxide by scavenging superoxide anion.

The presence of inflammation is an important element in the pathogenesis of atherosclerosis. Two pathways are activated during the process: the protein kinase C and nuclear factor-kappa B (NF- κ B) pathways. This leads to upregulation of genes that trigger the activation of angiotensin converting enzyme, the local production of angiotensin II and the expression of adhesion molecules on the surface of endothelial cells. These events can result in endothelial dysfunction. The most extensively studied biomarker of inflammation in cardiovascular disease is CRP. This is a circulating pentraxin that has a major role in human innate immune response and provides a stable plasma biomarker for low-grade systemic inflammation. It is predominantly produced in the liver. CRP has been implicated in multiple aspects of atherogenesis and plaque vulnerability, including expression of adhesion molecules, induction of NO, altered complement function and inhibition of intrinsic fibrinolysis. Procedures for its measurement are well standardized and automated and high-sensitivity assays (hs-CRP) are widely available. Increased CRP levels associated with increased prevalence of underlying atherosclerosis.

Studies of all Tunisian patients are nondialyzed chronic kidney disease, and with nondiabetic renal disease. Patients according to serum creatinine levels were sub-classified as follows: moderate renal failure, severe renal failure and end-stage renal disease. Etiologies of chronic renal disease in patients were chronic glomerular nephritis, chronic tubulointerstitial nephropathy, vascular nephropathy and unknown cause. Cardiovascular complications in all groups were diagnosed by echocardiography and electrocardiography. Patients with cardiovascular complications included cardiac insufficiency and left ventricular hypertrophy.

2. Homocysteine, paraoxonase activity and renal diseases

Homocysteine (Hcy) as a thiol-containing amino acid has gained great notoriety, since elevation of its plasma concentrations, a condition known as hyperhomocysteinemia, is correlated with many different diseases, in particular cardiovascular disease (Cavalca V et al., 2001, Kerkeni M et al., 2006), and end-stage renal disease (ESRD) (Ducloux D et al., 2000, Perna AF et al., 2004). Serum paraoxonase 1 (PON1) is an oxidant-sensitive enzyme that inhibits the atherogenic oxidation of low density lipoprotein (LDL). PON1 activity is also implicated in protection against cardiovascular disease (Mackness M et al., 2004). Some studies found that the paraoxonase protein (PON1), carried on high density lipoprotein (HDL), has homocysteine thiolactone (HcyT) hydrolase activity and protects against protein

homocysteinylation in vitro (Jakubowski H et al., 2000, Jakubowski H, 2000). A possible molecular mechanism underlying hyperhomocysteinemia involves metabolic conversion of Hcy by methionyl-tRNA synthetase (MetRS) to HcyT, which then reacts with lysine residues in proteins, damaging their structure and impairing their physiological activities. HcyT is known to be cytotoxic in experimental animals and induces apoptotic death and proinflammation process in cultured human vascular endothelial and in primary human umbilical vein endothelial cells (HUVEC) (Kerkeni M et al., 2006). The extent of HcyT synthesis and protein homocysteinylation in human vascular endothelial cells depends on levels of Hcy, methionine, folate and HDL that are linked to vascular disease. In addition, hyperhomocysteinemia and paraoxonase activity are involved in the development of cardiovascular complications in patients with chronic renal disease and in patients undergoing hemodialysis.

We reported in previous studies that hyperhomocysteinemia, oxidative stress and paraoxonase activity are risk factors for cardiovascular disease and the severity of coronary artery disease in Tunisian population (Kerkeni M et al., 2008). The association between chronic renal disease, homocysteine and paraoxonase activity have been taken into account, and we reported that the development of cardiovascular complications related to end-stage renal disease (ESRD) (Kerkeni M et al., 2009). The coexistence of a high level of Hcy and a low PON1 concentration increases the severity of renal disease. In hyperhomocysteinemia condition, Hcy occurs in human blood in several forms. The most reactive is homocysteine thiolactone which it's detoxifies by Hcy-thiolactonase activity of PON1. We hypothesize that HcyT can also increase cellular toxicity in renal function via protein homocysteinylation participates in glomerular sclerosis and in the development of ESRD.

3. Endothelial NO synthase, methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and renal diseases

Epidemiologic studies have shown that dyslipidemia, diabetes mellitus, obesity, hypertension, and cigarette smoking are risk factors for cardiovascular complications. Assessment of these metabolic or lifestyle risk factors has, however, been ineffective in incompletely predicting the severity of renal disease and the development of CVD, suggesting that specific genetic predisposition should also be taken into account (Nordfors L et al., 2002).

The vascular endothelium modulates blood vessel wall homeostasis through the production of factors regulating vessel tone, coagulation state, cell growth, cell death, and leukocyte trafficking. One of the most important endothelial cell products is nitric oxide (NO), which is synthesized from L-arginine by enzyme endothelial nitric oxide synthase (eNOS). NO plays a key role in the relaxation of vascular smooth muscle, inhibits platelet and leukocyte adhesion to the endothelium, reduces vascular smooth muscle cell migration and proliferation, and limits oxidation of the atherogenic LDLs. NO may modulate homocysteine concentration directly by inhibiting methionine synthase, the enzyme that synthesizes methionine from homocysteine and 5-methyltetrahydrofolate. Alternatively, NO may modulate Hcy concentrations indirectly via folate catabolism by inhibiting the synthesis of ferritin, a protein that promotes the irreversible oxidative cleavage of folate. Although low folate concentrations are associated with hyperhomocysteinemia, which is a risk factor for atherosclerosis, the relative contributions of these potential mechanisms to Hcy modulation in vivo remain unclear.

Glomerular microcirculation is involved in the deterioration of renal function. Among several factors that regulate renal hemodynamics, NO (nitric oxide) has been reported to be critical. In the vascular endothelium, NO is produced by endothelial NO synthase (eNOS). NO production can be influenced by polymorphisms of the eNOS gene. Polymorphisms in exons may alter the three-dimensional structure of the enzyme, and those in introns may change the transcriptional activity (Tesauro M et al., 2000). These can lead to a decrease in NO production and, subsequently, an increase in arterial pressure or intraglomerular hypertension and produce renal damage. Previous studies have shown the polymorphisms of the eNOS gene are associated with the progression of nondiabetic end stage renal disease (ESRD). Several polymorphisms have been identified in the eNOS gene, among which is one located in exon 7 (G894T), which modifies its coding sequence (Glu²⁹⁸→Asp). The G894T polymorphism was reported to be associated with hypertension, diabetic nephropathy and ESRD (Shin Shin Y et al., 2004). Furthermore, in ESRD, mean total homocysteine levels are commonly elevated, and the methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms may also be associated with renal disease. The eNOS and MTHFR gene polymorphisms have been shown to be associated with cardiovascular disease. We reported in previous studies that the eNOS and MTHFR gene polymorphisms were associated with the presence of cardiovascular disease (Kerkeni M et al., 2006a et b). However, the relationship between eNOS, MTHFR gene polymorphisms and cardiovascular disease in Tunisian patients with chronic renal disease has been examined. We investigated that (a) the relationship of these gene polymorphisms with the presence and the severity of renal disease, and (b) their relationships with CVD in these patients (Kerkeni M et al., 2009).

4. The mechanisms of homocysteine and paraoxonase activity to induce renal diseases

In our studies, prevalence of hyperhomocysteinemia was present in 94 % of Tunisian patients. We found that an increased Hcy levels in patients with moderate renal failure to ESRD. This observation was showed by numerous clinical studies, but the pathogenic role of increased Hcy Levels in the progression of ESRD remains controversial and the mechanisms how Hcy induced renal toxicity are still unknown. Recent studies showed the pathogenic action of Hcy in the glomeruli or in the kidney, such as local oxidative stress, endoplasmic reticulum stress, homocysteinylation, hypomethylation and glomerular mesangial cell apoptosis via activation of p38-mitogen-activated protein kinase (Yi F and Li PL, 2008). In hyperhomocysteinemia condition, Hcy occurs in human blood in several forms. The most reactive is homocysteine thiolactone (HcyT). It spontaneously homocysteinylates proteins impairing their structures and functions. An increase in HcyT can itself lead to inactivation of PON1 as it has been demonstrated by in vitro studies or negatively regulate PON1 gene expression. Furthermore, we showed in previous study that HcyT might possess stronger cytotoxicity and pro-inflammation properties in primary human umbilical vein endothelial cells. We hypothesize that HcyT can also increased cellular toxicity in renal function via protein homocysteinylation. There is considerable evidence that protein homocysteinylation participates in glomerular sclerosis and in the development of ESRD. In this regard, Perna et al. have reported that plasma homocysteinylation increased in ESRD patients subject to hemodialysis (Perna AF et al., 2006). It was demonstrated that in patients with terminal renal failure without dialysis protein homocysteinylation is significantly enhanced which may contribute to the

atherogenesis and progression of ESRD in these patients. Another interesting mechanism that possibly mediates glomerular injury or sclerosis induced by homocysteinylated proteins in connective tissue proteins are especially susceptible to Hcy and HcyT attacks.

Hyperhomocysteinemia and a low PON1 activity were associated in patients with each etiology except the unknown cause. We showed an increased Hcy level in patients with chronic tubulointerstitial nephropathy than patients with glomerular nephropathy. Hyperhomocysteinemia is able to promote glomerular damage and generate tubulointerstitial lesions. O'Riordan et al. showed that chronic endothelial nitric oxide synthase (eNOS) inhibition actuates endothelial mesenchymal transformation in chronic kidney disease (O'Riordan E et al., 2007). Several studies have demonstrated that the bioavailability of NO is decreased in hyperhomocysteinemia. In addition, we found that patients with vascular nephropathies showed an increased hyperhomocysteinemia than patients with glomerular nephropathy. Hyperhomocysteinemia and a low PON1 activity were markedly associated in CRD patient with cardiovascular complications including cardiac insufficiency and left ventricular hypertrophy. Some studies have shown that hyperhomocysteinemia induced hypertension and ventricular hypertrophy. Given the similarity of pathological changes between glomerular injury and Hcy induced arterial damages, such as endothelial injury, cell proliferation or growth, increased matrix formation, and aggregated proteoglycan, it is assumed that an increase in plasma Hcy levels may also directly act on glomerular and tubulointerstitial cells, resulting in glomerular damage and tubulointerstitial lesions. Moreover, an impaired renal function will lead to a further increase in plasma Hcy levels which in turn exaggerates the progression of glomerular injury, resulting in a vicious cycle and consequent glomerulosclerosis and ESRD. In addition, Hcy may also produce detrimental actions or increase the risk of cardiovascular disease by decreasing plasma or tissue adenosine levels. It is well known that adenosine evokes several biological actions in the cardiovascular system and participates in the regulation of the renal function, including renal glomerular perfusion. It was demonstrated that chronic elevations of the plasma Hcy concentration in rats resulted in atherosclerotic changes and glomerular dysfunction and sclerosis accompanied by sustained low level of plasma adenosine. Decreased adenosine concentrations during hyperhomocysteinemia may be due to an enhanced activity of a bidirectional enzyme, S-adenosylhomocysteine hydrolase. Due to space limitations, some other interesting topics related to the possible mechanisms mediating Hcy-induced glomerular and tubulointerstitial toxicities are not included, such as activation of proinflammatory factors, increased homocysteine thiolactone levels, and Hcy induced abnormal mitochondrial biogenesis.

5. The mechanisms of the eNOS and MTHFR gene mutations to induce renal diseases

We reported an association between the common G894T polymorphism of the eNOS and the presence of renal disease. We found that the eNOS 894T allele was markedly associated with severity of renal disease in patients with nondiabetic renal disease. Furthermore, eNOS G894T mutation was increased in CRD patients with cardiovascular complications including cardiac insufficiency and left ventricular hypertrophy. In the vascular endothelium, NO is produced by eNOS and implicated in numerous aspects of renal vascular control and function. It is thought to exert a vasculoprotective effect by modulation of kidney blood flow

through counterbalancing the effects of the renin-angiotensin system. A deficiency of the endogenous vasodilator NO has been implicated as a potential cause of chronic renal diseases and in end-stage renal failure. NO production can be influenced by polymorphisms of the eNOS gene. These can lead to a decrease in NO production and, subsequently, an increase in arterial pressure or intraglomerular hypertension and renal damage. Polymorphisms in exons may alter the three-dimensional structure of the enzyme, and may change the transcriptional activity (Tesauro M et al. 2000). The eNOS G894T variant leads to an amino acid substitution of aspartate for glutamate at position 298 of the protein. Tesauro et al. showed that an *in vitro* study the eNOS protein with aspartate, but not glutamate, at position 298 is subject to cleavage by endogenous protease and produces 35-kDa amino-terminal and 100-kDa carboxyl-terminal fragments. Nevertheless, Tesauro et al. found that significant potential structure changes in the Chou-Fasman secondary structure and pointed out that the coding region polymorphism has functional consequences.

We therefore speculate that, *in vivo*, the eNOS 894GT and 894TT genotype leads to alter NO production, endothelial dysfunction, promotes renal hemodynamic dysfunction, and aggravate the extent of renal disease. With chronic eNOS enzyme dysfunction, decreased NO production may contribute to raise cardiovascular complications as well as micro and macrovascular damage. Previous studies were interested the effect of MTHFR genotypes on total homocysteine in patients with renal failure. However, plasma total homocysteine increases as renal function declines; it is elevated in the vast majority of patients with ESRD. The glomerular filtration rate is a strong determinant of plasma homocysteine concentration, even in individuals with very mild renal dysfunction. As reviewed by Brattström and Wilcken, almost every study in which renal diseases has shown a highly significant positive correlation between serum creatinine and Hcy concentrations. The total Hcy levels increase in patients with moderate renal failure and can be $>100 \mu\text{M}$ in patients with ESRD. Nevertheless, several studies showed that MTHFR C677T polymorphism aggravates hyperhomocysteinemia in hemodialysis patients. However, the association between MTHFR polymorphisms and the risk of cardiovascular disease in patients with renal disease remains controversial.

In our studies, MTHFR polymorphisms were not associated with the presence and the severity of renal disease in CRD patients, and we found also a lack association with cardiovascular complications in CRD patient. On the other hand, hyperhomocysteinemia was founded in these patients, and Hcy levels increased not only in ESRD patients but increased markedly in patients with cardiovascular complications. We hypothesize that the synergic effects of the eNOS G894T variant and hyperhomocysteinemia induced less NO production and contribute to the extent of severity of renal disease and induced cardiovascular damage.

6. Conclusion

Hyperhomocysteinemia and low PON1 activity are associated with chronic renal disease and markedly associated in Tunisian patients with cardiovascular complications. We postulate that with chronic toxicity induced by hyperhomocysteinemia may contribute to the severity of renal disease and increase the incidence of cardiovascular disease in patients. Some key targets in these pathogenic pathways must be identified to direct toward prevention or treatment of ESRD associated with hyperhomocysteinemia which is particularly important since so far there are no efficient Hcy lowering and Hcy detoxifying

strategies being used in CRD patients. The G894T polymorphism of the eNOS gene is associated with the presence and the severity of renal disease in Tunisian population. The eNOS G984T variant and hyperhomocysteinemia both increase the extent of renal disease, and the development and progression of cardiovascular complications.

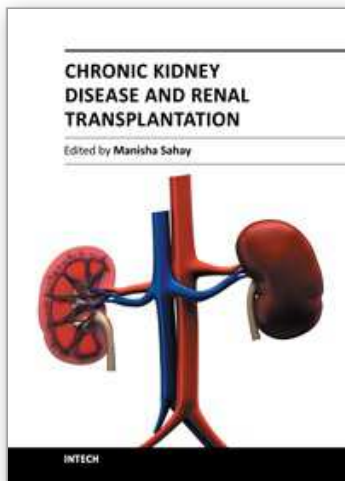
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This valuable resource covers inpatient and outpatient approaches to chronic renal disease and renal transplant with clinical practicality. This first section of the book discusses chronic disease under distinct topics, each providing the readers with state-of-the-art information about the disease and its management. It discusses the fresh perspectives on the current state of chronic kidney disease. The text highlights not just the medical aspects but also the psychosocial issues associated with chronic kidney disease. The latest approaches are reviewed through line diagrams that clearly depict recent advances. The second section of the book deals with issues related to transplant. It provides effective and up-to-date insight into caring for your transplant patients.

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