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PROGRESSION OF CHRONIC RENAL FAILURE AND OXIDATIVE STRESS

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INTRODUCTION:

Chronic renal insufficiency (CRI), once established, tends to progress to end-stage failure. Progression occurs even when the process or primary lesion has been treated or this is apparently inactive. That means that alterations and transformation in surviving nephrons, produced finally lost by this nephrons and outcome the chronic renal insufficiency. The efforts to stop or even slow the progression of CRI likely have been unsuccessful[1].

Mechanisms underlying the progression of renal disease have remained obscure for various reasons: The kidney responses to a variety of insults in a similar manner. Multiple pathogenetic mechanisms converge on a common avenue of sclerosis, by which specialized cellular structures are replaced by fibroblasts, collagen and mesenchymal matrix, and it is usually impossible to elucidate the cause of the CRI[1]. Traditional, the most important factors affecting the process of progressive renal disease and glomerulosclerosis appear to be systemic hypertension, dietary protein daily intake, proteinuria, elevation in serum lipid levels and glomerular hypertrophy[1].

Systemic hypertension has adverse effects on the kidney and may initiate the development of renal disease o accelerate loss of function in the kidney in which parenchymal disease is already established. The control of hypertension reduced the progression of renal disease, and the effect appears to be maximal in those patients with proteinuria. Numerous studies[2] has showed a slower rate of renal disease progression, whit the use of angiotensin-converting enzyme (ACE) because their antiproteinuric effect. These effects were independent of blood pressure control.

For many years, it was assumed that the degree of proteinuria was an indicator of severity of damage

within the glomerulus. However, in the past two decadas, it was recognized that proteinuria may also contribute to the progressive nature of many renal diseases. The degree of proteinuria has been associated with the rate of progression of renal disease[2]. Protein restriction slows progression of renal disease howewer their application has been controversial because their adverse nutritional effects.

There are two mechanism by which lipid may exacerbate the progression of chronic glomerular disease: First, the accumulation of lipid in the mesangial cells may result in the development of focal glomeruloesclerosis. Second, low-density lipoproteins can induce the adherence of monocites to endotelial cells.

Glomerular hypertrophy, which lead to subtotal nephrectomy, is invariably associated with glomerular sclerosis in remnant nephrons. That is attributed to abnormal hemodynamics besides to growth factors [1].

In addition to this classic factors in last years one consider that oxidative stress was other important factor in pathogenesis of chronic renal disease. In fact, along last years oxidative stress one has been showed an important pathologic mediator in divers and many clinic sites as carcinogenesis, atheroesclerosis, cardiovascular diseases and hypertension, neurodegenerative disease and aging[3], [4].

Besides the oxidative stress, from nephrologic view, play a major role in many clinical and experimental diseases[3]:

- **In glomerular diseases like membranous glomerulonephritis, Ig A nephropaty, antibasement membrane glomerulonephritis or minimal-change nephropathy[5], [6].**
- **In post-ischemia acute renal failure o drugs as acetaminophen,aminoglucosides and cephalosporins [7].**
- **Changes involved in renal transplant.**
- **Obstructive uropathy and pielonephritis.**
- **Funtional impairment link to renal extirpation and chronic renal failure[8],[14],[16].**

Most of this studies has been support directly to count of oxidants products, indirectly by the detection of products of lipid peroxidation in renal tissues and thereby protective effects by renal function of administered antioxidants in experimental models [9], [5].

We say, brevity, that oxidative stress appair in tissues and cell when exists a disbalance between proxidantns and oxidants species to favour this premiers. The most important oxidative species in biologic systems are the reactive oxygen species (ROS), whit are intermediator species by chemical reactions. ROS are different others chemical species since they have unpaired electron on outer shell. So, ROS are very unstable and reactive and have great adhesion for electron to complete the shell, such ROS attack other molecular structure was very destroying. The most important ROS are superoxide anion (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical, singlet oxygen ($1O_2$-) and hypoclorous acid (OHCL).

There are endogenous and exogenous antioxidants systems which limit activity and ROS production and maintenance control system. The most important antioxidants endogenous system was superoxide dismutase, catalase and glutathione peroxidase. The glutathione antioxidant system is formed by reduced glutathione and glutathione reductasa enzyme activity which reduced systematic oxided glutation; Transferrin and ceruloplasmin are antioxidants proteins. Antioxidants exogenous are vitamins A, C and E, and copper and selenium metals, this as cofactor by glutathione peroxidasa enzyme[8],[9],[16].

Conditions of increased ROS production are inflammation, hyperoxia, ischemia-reperfusion sequence, metabolism of drugs and radiation exposure[3]. It is well established that imbalance ROS-antioxidants species may induced functional and estructural derangements every localization.

At general way, ROS initiate to poliinsatured lipid acids (very abundant in all cells and as much susceptible as much insatured) a chain of reactions, which is know as lipid-peroxidation, and finally can lead to alterations in biological membranes. ROS interaction whith proteins lead to oxidation lateral aminoacids, that can promote lost or modification at biological function. In addition ROS may

react whith all nucleic-acids compounds specifically can produced oxidations of nitrogened bases, and originating mutations.

Studies in patients whit varying degrees of kidney impairment suggest that patients with chronic renal disease are in a state of oxidative stress compared with healthy controls, and the degree of oxidative stress is correlated whit degree of renal failure[10,11,12]. In addition, there are studies which have shown elevated antioxidant activity when oxidative stress environmental is high [13,14]. This studies clearly demonstrated that antioxidant activity are enhanced following to high oxidative status, to purpose for incomplete recovery the cellular homeostasis.

ROS are involved in progressive renal injury and this is supported by several lines of evidence[15]:

- **Increased generation of oxidants occurs in chronic renal injury.**
- **Various antioxidants strategies exert beneficial effects in models of chronic renal injury.**
- **Oxidative stress can induce changes in inmanipulated kidney that resemble those seen in chronic renal disease[15].**

ROS production in the kidney:

Cells of renal structures so vascular (endothelial and smooth muscle cells), as glomerular (endothelial and mesangial) and tubular (proximal, distal and collector), are capable to produce and secreting ROS for stimulating factor like drugs, acute hypertension, radiation exposure and hyperoxia.

In addition, circulating infiltrating cells (granulocytes, monocyte-macrophages and platelets), which are present in many inflammatory renal process (vasculitis, glomerulonephritis, pyelonephritis),are capables to produce large amounts of ROS. Therefore, it is impossible to separate the role of ROS produced by infiltrating from the ROS produced by resident cells in an attemp to evaluate the ROS action in renal disease[16].

Among stimuli able to elicit ROS production in neutrophils are bacteria, immunocomplexes, the fraction C5a of complement, platelet-activating factor (PAF) and interleukin-1. In macrophagos, as well as in neutrophils Tamm-Horsfall protein and ANCA may get ROS production. In platelets ROS production may occur during arachidonic acid metabolism, therefore stimuli able to trigger this metabolism could elicit ROS production.

Mechanisms of renal damage:

ROS may contribute to progressive renal disease by virtue of several mechanisms:

- **Haemodynamic actions by impairing glomerular permselective properties.**
- **By inducing inordinate or aberrant growth responses.**
- **By causing loss of cellular phenotype and apoptosis.**
- **By promoting acute and chronic inflammatory responses: The oxidants can upregulated certain adhesion molecules and proinflammatory mediators and the transcription factors and fibrogenic cytokine incriminated in progressive renal injury[15].**
- **In surviving nephrons after loss of renal mass, one produced increased on oxygen consumption, that lead to enhaced oxidative stress potencialmente injurious for this nephrons[17, 18].**

In adittion, activity surviving tubules increased, because the oxygen consumption and ROS production increasing.

In basal conditions, it can be present a permanent damage promoted for ROS, whith in specifically conditions, can enhaced for an increasing local metabolism and ROS production.

This could be the case for protein overload, because it induces a most oxygen consumption in surviving nephrons and increasing ROS production and accelerating renal damage [16, 18].

At the glomerular sites ROS induce, in pathological settings as glomerulonephritis,microthrombotic and microangiopathic processes and toxic damage (drugs, radiation), morphological changes as edema, desquamation of endothelium and denuding of basement membrane, thrombi, mesangiolysis, foot process fusion and epithelial vacuolization. Functional changes consist in increased permeability whit proteinuria and changes in intraglomerular hemodynamics.

At the tubular site ROS may iniciate swelling, detachment from the basement and lysis. Functional changes are increasing permeability, alteration in transmembrane potential and proliferative response. This lesions are present in reperfusion injurie, toxic damage (gentamicin, cisplatinum) and pigment cats.

At the vascular site morphological changes are edema, desquamation of endothelial cells and thrombi. As a consequence, it is produced an altered vascular reactivity, increased permeability, enhanced inflammatory cells adhesion and proliferation of smooth muscle cells. A role of ROS in a pathological setting has been suggested, in microthrombotic and microangiopathic processes, in hypertensive disorders and arterioesclerotic processes.

HYPOTHETIC TERAPEUTIC IMPLICATIONS.

Antioxidants administration:

Selenium is a cofactor of enzyme antioxidant glutathione-peroxidase. Deficiency of selenium causes a reduction in the activity of this enzyme resulting in increased oxidative stress. Selenium deficiency has been shown to cause proteinuria and glomerular esclerosis in rats. Proteinuria induced in rats by aminonucleoside of puromicin was prevented by selenium and vitamin E supplementation. Human studies suggest that deficits or supplementation of selenium and vitamin E play a role in fisiopathology of renal complications in diabetic and non diabetic patients[18,19].

Dietary protein:

Protein overload enhace the oxygen consumption in surviving nephrons in subtotal ablation renal model[17], in addition, increase the ROS production. So, protein restriction may result beneficial in this situation. Other mechanism that contribute to progressive renal damage is toxicity at the tubular site of filtered proteins [20]. Dislipemia control:

Lipoproteins and lipid peroxidation can be important modulators in progressive kidney disease. A studie has showed total cholesterol levels and LDL-cholesterol levels were higher in patients whit varying degrees of kidney impairment than control group. On the contrary HDL-cholesterol level decreased whith progression of renal disease[11]. As an additional pathway of injury one may considerer the effects of lipids bound to proteins (albumin and lipoproteins, including oxidized low density lipoproteins), which are potent cytotoxic molecules by inducing an oxidative stress.

Arterial hypertension:

ROS are being recognized actually to be important mediators of vascular damage in hypertension. When one elects a drug for hypertension we should consider that angiotensin-converting enzyme inhibitors (ACE) and carvedilol have demonstrated antioxidants properties in addition of control blood pressure[21].

Iron supplementation:

In experimental subtotal nephrectomy it has been shown that in tubular cells the greater damage, the higher the intracellular iron content. The iron represents a substrate for ROS production because their facility and capacity oxidation-reduction, and their catalytic role in Haber-Weiss reaction, to generate hydroxyl radical [16, 22]. In experimental models of progressive renal disease in rats, those with low iron diet had significantly lower proteinuria and developed less glomerular sclerosis. In addition, at experimental models, the restriction iron diet and employing iron quelantes, slackens tubulo-interstitial fibrosis[23].

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Comment Reviewer 1: Prof. José Fuentes Oro, MD. Secretario Academico del Instituto Universitario de Ciencias de la Salud. Fundacion Hector A.Barcelo, La Rioja. Argentina

The terminal chronic renal failure cause a huge economic, social and human impact to the patient relatives and familiars. There are in the world more than 500000 sick people submitted to a substitute treatment of the renal function. From them, 70% receive haemodialysis treatment, a 9% continuos ambulatoty peritoneal dialysis and 21% has a functional renal transplant. The world's distribution of this treatment has a strong relationship with the economic development level: 37% of the patients receive a treatment in USA, 33% in Western Europe, 21 in Japan and only 9% in Africa, Latin America and Eastern Europe[1].

Many diseases may produce renal damage and lead to a chronic renal failure (CRF). It progression to a terminal stadium may take place although the original pathology is inactive.

In this article Basilia Gonzalez Diez MD makes a detailed revision of the possible progress causes of this disease. She lists the already known mechanisms and introduce us to the analysis of a new factor in the progression of the CRF: the oxidative stress.

The production of Reactive Oxygen Species (ROS) is a natural process, a biological constant. They are made to do physiological events, but if they are generated in an inappropriate form or in excess they may have toxics effects that are aggravated in presence of transitions metals such as steel and copper. The excess of this species may cause damage to the DNA, lipids, proteins, cell's carbohydrates and there are known numerous clinical conditions in which they involucrate.[2]

The term ROS describe products form O2 that aren't used in the ATP synthesis and include two groups: the free radicals with the superoxide anion, the hydroxyl radical and the alcohoxil radical and the not radicals derivates hydrogen peroxide , hypoclorous acid, the singlet oxygen and the ozone. To this nocive species the body put up antioxidants defense mechanisms like the superoxide dismutase, catalase enzymes, vitamins like B-carotene, the vitamin E or metals like the selenium, copper or zinc and transition's metals transporters. [3], [4], [5]

When the equilibrium between free radicals and antioxidants breaks in favor of the first ones it produce pathological processes associated to several diseases.

All this "new world" in the comprehension of the CRF, it progression to the terminal phase and its possible therapeutics implications is described with solvency by the author in this article.

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Comment Reviewer 2: Dr. L Ibanez-Valdes, MD Department of Family Medicine. University of Transkei. South Africa.

It was a great sense of delight to received the article entitled: "Progression of chronic renal failure and oxidative stress" for review.

We found (Prof. Foyaca and myself as peer reviewed) that this manuscript will be suitable for publication after some minimal correction such as:
1.- The list of references should be enumerated.
2.- The references used should listed by alphabetic order or in order to appearances and not like this: "...and chronic renal failure (8,14,16)" if the references: 14 and 16 were not previously mentioned.
3.- The word of "Bibliografia" should be change by "References" or "Bibliography"

We would like to thanks to the author for the effort made and her contribution to the good quality of this Journal.

Comment Reviewer 3: Pedro Abaigar Luquín, MD. PhD. Nephrologist. Hospital General Yagüe. Burgos. Spain

In this article we can read a clinical review about one of the topics more attractive which is involved in the progression of chronic renal deases.

The author makes a revison about the phisiopathology and the implications of several well known causes of progression of renal deseases. First, she brievely describes what the stress osidative is and what the reactive oxygen species are, second their implication in most of the process of developping chronic renal deseases and finally the hypothetical therapeutic implications.

She makes an appoinment at the oxidative stress reactions are the end of many pathological condition on the path to the end of renal desease, wathever would have been the first or the initial pathological injury (glomerular,tubular or vascular).

When one read this article, it can be had in mind a clinical and clear idea about the possibility that stress oxidative could have a central role in the deleterious effect of all kind of renal insults.