Hypertension and dyslipidemia in the pathophysiology of chronic kidney disease

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Submitted: 18 October 2008
Accepted: 11 November 2008

Arch Med Sci 2009; 5, 3A: S 395–S 414

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Abstract

This review focus on the natural history of chronic renal disease associated with hypertension and will discuss separately the renal disease hypertensive emergencies, hypertension in association with preexisting renal disease and mild hypertension in patients with normal kidneys. Chronic renal disease results in profound lipid disorders, which derive largely from dysregulation of HDL and trygliceride-rich lipoprotein metabolism. A specific mention of is made of patients with a deficiency of LCAT and patients with abnormal variants of Apo E in relation to the lipid-induced chronic renal damage. We discuss the pathogenetic mechanisms involved in the hypertension-induced and dyslipidemia-induced renal damage and the hypertension and lipid disorders resulting from renal disease.

Key words: inflammation, renin-angiotensin system, statins, renoprotection.

Pathophysiology of chronic renal failure induced by hypertension

Natural history of hypertension-induced renal damage

The association between increased pulse pressure and stroke were noted already in the 18th century when Giovanni Battista Morgagni described the clinic pathological characteristics of the apoplexy suffered by a in a patient he shared with Maria Antonio Valsalva and found "his pulse frequent, large and vehement" and further commented that the characteristics of the pulse were not "of the least advantage" in this condition [1]. However, afterwards and up to the first half of the 20th century the increased blood pressure was considered an adaptive response necessary for the perfusion of vital organs. In 1931, cardiologists discouraged the treatment of hypertension and Hay wrote that "the greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it" [2]. Changes in this perspective took place about half a century ago when it was realized that high blood pressure could be dangerous in specific situations and authoritative textbooks of medicine stated that the treatment of hypertension should be confined to patients who presented "chest pain or other signs of overt signs of disease" and "other should not be treated" [3]. The term "benign" essential hypertension was coined to define a condition that had a minor clinical significance in contrast with the "malignant" course that was associated with severe hypertension resulting in organ damage.

Much has changed since that time and, as stated by Moser [4], the management of hypertension in the 21st century represents a major success story in preventive medicine resting on the demonstration that the lower the blood pressure (BP), the better the outcome, regardless of how it was achieved.

In recent guidelines [5] the term "malignant" hypertension that defined severe hypertension associated with severe retinopathy with papilledema [6] and was previously reported to occur in 1% of hypertensive patients [7], has been abandoned and replaced for the definition of hypertensive crises that comprise hypertensive emergencies, associated with acute end-organ damage requiring immediate treatment, usually in the Intensive Care Unit, and hypertensive urgencies, that need correction in hours or a few days. In hypertensive crises the reduction of blood pressure will halt, prevent or reverse the rising levels of azotemia.

Numerous studies have demonstrated that the incidence of stroke and myocardial infarction is directly related to the blood pressure levels and recent guidelines for blood pressure control [5], recognize the impressive reductions in cardiovascular morbidity and mortality obtained by reduction in blood pressure levels [8-13]. Similar reductions in the incidence of end-stage renal disease (ESRD) with better blood pressure control have not been registered [14] and beneficial effects on renal function obtained by lowering blood pressure in patients with mild to moderate essential hypertension remain controversial [15]. Nevertheless, the association between ESRD with severe hypertension has been amply documented. Landmark studies have shown that that the risk of ESRD was nearly 50 times higher if systolic blood pressure was higher than 200 mm Hg than if it was 120 mm Hg [16] and serum creatinine values are 3 times higher in patients with diastolic blood pressue higher than 115 mm Hg with respect to those with 90 mm Hg [17]. In addition, there is also compelling evidence from interventional trials that in patients with mild to moderate renal disease, there is a direct relationship between the degree of reduction in blood pressure and the retardation of renal functional loss.

Therefore the natural history of chronic kidney disease (CKD) resulting from hypertension will be discussed in three different clinical situations: hypertensive crises, hypertension in association with co-existing renal disease and hypertension in patients without evidence of renal disease.

Hypertensive crises

Severe hypertension, usually with levels of ≥ 180/120 mm Hg associated with or without acute end-organ damage (chest pain, myocardial infarction, cerebrovascular accident, hypertensive encephalopathy, papiledema, uremia, hematuria) may occur in patients not previously known to be hypertensives and in patients with primary (essential) or secondary hypertension. The majority of the cases of secondary hypertension are associated with renal parenchymal (glomerular or tubulointerstitial) or renovascular disease. Renal functional impairment is usually present and the characteristics of the urinary sediment and the degree of proteinuria depend on the preexisting renal disease.

The pathophysiology of the renal injury in hypertensive crises results from the mechanical stress of the increased pressure on the vessel wall. The mechanical injury causes endothelial damage and inflammation with local activation of mediators of inflammation and components of the coagulation cascade. The old observation that patients with chronic hypertension may tolerate higher levels of blood pressure than previously normotensive individuals or patients with mild hypertension was attributed to the relative protection offered by the arterial wall hypertrophy that is commonly associated with long-standing hypertension [7]. The renal renin-angiotensin system (RAS) is activated in most hypertensive crises and was the rule in the previously designated "malignant" hypertension. The increased RAS activity not only induces a generalized vaso-constriction but, in addition, stimulates a large number of proinflammatory cytokines and exacerbates oxidative stress and local inflammation, all of which contribute to amplify the local damage.

Blood pressure control is mandatory in hypertensive crises. Before effective antihypertensive drug therapy was available the mortality of malignant hypertension was 40-80% in one year [18] and uremia accounted for 50% of the deaths [7]. Therapeutic advances have improved the prognosis but hypertensive crises remain a serious condition with a 5-year survival rate of only 80% [19]. Despite the widespread availability of dialysis, renal failure remains and important cause of death [20].

Clinical considerations: The treatment of malignant hypertension is outside the limits of this revision. From the view point of renal functional recovery is worth emphasizing the need to control the blood pressure and, in relation to prevent progression of CKD, the need to have a long-term inhibition of the renin angiotensin system (RAS) activity. There are no specific studies addressing the long-term effects of RAS blockade after hypertensive emergencies but it is reasonable to assume its beneficial effects in the management of hypertension that has previously resulted in renal

damage. A word of caution is necessary with respect to the use of angiotensin converting enzyme inhibition (ACEi) and or angiotensin receptor type 1 blockade (ARBs) in the early stages of hypertensive crises since it may result in further impairment of renal function because the suppression of angiotensin II (Ang II)-induced vasoconstriction it may reduce renal blood flow, especially in cases or renal artery stenosis.

Hypertension in association with renal disease

The incidence of ESRD associated with hypertension has increased steadily in the past decades despite a reduction in the mortality from cardiovascular disease attributed to the better control of the blood pressure in the population. At the present time hypertension represents the second cause of ESRD after diabetes [21] and plays a contributory role in the CKD caused by diabetes. Hypertension is present in 83% of the patients with CKD and 95% of those with ESRD and is even more frequent and severe in African Americans, males, obese and elderly individuals [22]. Increased prevalence of hypertension is associated with decreasing estimates of glomerular filtration rate (GFR) at intervals of 10 ml/min/1.73 m^2, irrespective of age, obesity and microalbuminuria [23]. In children, the prevalence of hypertension in CKD ranges from 20 to 80% depending on the severity of renal insufficiency and the underlying renal disease [24].

The association between CKD and hypertension is also reflected in population studies that found a strong association between the prevalence of hypertension and ESRD [25] and prospective studies that found that every 20 mm Hg increase in diastolic pressure even in the range of the normal blood pressure range resulted in a twofold increase in risk of developing an increased serum creatinine [26]. The relationship between the blood pressure levels and the rate of GFR reduction has also been noted in children [27].

The causal relationship between hypertension and CKD progression has been strongly suggested by a large number of observational [8, 16, 26, 28-31], and interventional studies [32-36] particularly in patients with chronic renal disease [37-41] including type I diabetics [42, 43], type II diabetics [44] and non-diabetic patients [40, 45-47].

Several studies have also shown that there is a relationship between the blood pressure reduction achieved by treatment and the reduction in the rate of progression of renal insufficiency [48] even within the normal blood pressure range [28, 49]. Prospective analyses also have determined that within the normal range, higher blood pressure levels are associated with a higher incidence of proteinuria [50].

Taken together, these studies are compelling evidence that not only from he point of view of cardiovascular disease but also from the perspective of renal disease, the blood pressure levels that define hypertension as a pathologic condition need to be lowered, as it is now recognized by the guidelines of the Joint National Commmitte in the US (JNC7) [51] and the European Hypertension Society [52] that blood pressure targets should be < 130/80 mm Hg in adults. In children, the presently recommended blood pressure levels should be < 90^{th} percentile of normal values adjusted for age, gender, and height [53].

The beneficial effects of blood pressure reduction are more evident in proteinuric patients, especially in those with severe proteinuria (> 2 g/day) [53-57] but likely extend to lower levels of proteinuria. In an analysis of the data collected in the AASK trial, the magnitude of the reduction in proteinuria in the first 6 month predicted subsequent progression of CKD and this effect extended to participants with baseline urinary protein levels of less than 300 mg/day [58].

Various components of blood pressure have been evaluated as predictors of risk of progression of CKD. While all of them (systolic, diastolic and mean blood pressure) and even the lack of night reduction in blood pressure levels (non-dippers) have been associated with CKD progression [59-61], prospective studies have found that systolic blood pressure is the most useful clinical measurement since the others offer no added advantage [62].

A number of studies have addressed the question of the type of antihypertensive medication that would result in better renal outcomes in patients with diabetes. Angiotensin converting enzyme inhibition (ACEi) and ARBs are intuitively drugs of choice because of their potential of not only control the blood pressure but also reduce the non-hemodynamic actions of Ang II. In diabetic nephropathy, type I and type II, a large meta-analysis of 100 randomized and non randomized trials published in 1993 [63] concluded that lowering of the blood pressure by any drug therapy slowed the progression of renal disease but ACE inhibition offered benefits independent of blood pressure reduction. A prospective randomized trial of 409 patients with type I diabetes confirmed the beneficial effects of ACE inhibition in relation to doubling the serum creatinine [64] and more recently, the beneficial effects were also observed in diabetic patients with microalbuminuria and normal blood pressure [65-69]. In two recent prospective randomized trials of patients followed for a mean of 3.4 years [70] and 2.6 years [71] the treatment of diabetic patients with ARBs resulted in a 25 to 33% reduction in the doubling of serum creatinine and 28 to 23% reduction in ESRD, respectively.

In non diabetic patients, Zuchelli *et al*. [40] found that after 3 years of treatment, less patients receiving captopril reached ESRD than patients receiving a calcium channel blocker and similar results were obtained with enalapril vs. a β-blocker by Hannedouche *et al*. [72].

Recently, a new oral renin inhibitor, Aliskiren, has been approved for the treatment of hypertension. This drug has antihypertensive and renoprotective effects in the streptozotocin-diabetic TG (mRen-2) 27 rats, reduce prorenin expression in the glomeruli, tubule and cortical vessels and may block prorenin-induced angiotensin generation [73]. In humans, Aliskiren induce a renal blood flow and natriuresis increment that exceeds that observed with ACEi and ARBs [74]. Reduction in plasma rennin activity (PRA) is not modified by the concomitant administration of other antihypertensive drugs and diuretics and the blood pressure lowering effects persist 2-3 weeks after stopping the drug [75]. In a recent double-blind, randomized study, Aliskiren (150 mg daily for 3 months follow by 300 mg daily for 3 months) induced a modest reduction in blood pressure and an impressive reduction in the proteinuria, as determined by the albumin-creatinine urinary ratio, in patients receiving losartan, indicating the potential for beneficial effects over and above those obtained with ARBs alone [76].

Despite the enormous efforts devoted to highlight the need of blood pressure treatment, the progress made has been mostly evident so far in the public consciousness of hypertension as a public health problem and much remains to be achieved in relation to blood pressure control. In the study of Serafidis *et al.* of the patients in the KEEP investigation [77] awareness and the prescription of treatment were high (80.2 and 70.0%, respectively), but the blood pressure control (< 130/80 mm Hg) was only 13.2%, and poor control was particularly prevalent in obese, African Americans and males.

Clinical considerations: Epidemiological and clinical studies have consistently shown that hypertension is associated with CKD and when present in these patients leads to progressive renal failure. The causal association of high blood pressure and CKD progression is very strong when the blood pressures are high (stages 11 to IV) and when the hypertension is present in association with CKD of any etiology. The target blood pressure levels should be < 130/80 and reduction in proteinuria is a major goal in the treatment of hypertensive patients with CKD. Two or 3 antihypertensive drugs are required to treat blood pressure in patients with CKD and one of these drugs should be directed to suppress the renin-angiotensin system. A frequently useful combination includes a thiazide diuretic and ACEi or ARB and future studies may confirm the findings in recent studies that indicate that oral renin inhibition, alone or in combination with ARBs may be beneficial in diabetic nephropathy.

The role of diuretic therapy and dietary salt restriction in the management of hypertension in patients with CKD is beyond the scope of the present revision.

Hypertension as a primary cause of chronic kidney disease

The role played by the kidney in the pathophysiology of salt excretion in the development of increased blood pressure levels has been extensively investigated and the existence of hypertension in a large number of conditions, both experimental and clinical, that have in common a tendency to salt retention give solid ground to the causal relationship between kidney disease and hypertension [reviewed in 78]. Precisely in the fact that renal disease causes hypertension resides the difficulty in establishing if benign hypertension causes CKD because it is difficult, or perhaps impossible, in the myriad of studies available in the literature to identify which patients followed to specific endpoints (usually doubling of serum creatinine or ESRD) had preexisting renal functional impairment.

Perneger *et al*. [79] has lucidly defined the difference between conditions that initiate and conditions that promote or influence the progression to CKD. In the case of hypertension, the critical data to address this issue may not be derived from observational studies that would only record an association between hypertension and renal failure. Longitudinal studies by Shulman *et al*. [35] and Klag *et al*. [80] suggested that non-malignant hypertension may lead to CKD but these studies include a significant number of African American patients that are known to have susceptibility to hypertension-associated renal damage and, more important, the existence of baseline underlying renal disease was not excluded. Iseki *et al.* [81] found that in their study of the risk of developing CKD in a mass screening cohort that proteinuria, elevated serum and higher baseline blood pressure progress more frequently to ESRD; however, when the data was adjusted for baseline renal dysfunction, the relationship between blood pressure and ESRD was abolished.

The potential role of hypertension as initiator or accelerate the progression of CKD was examined by Hsu [82]. In a critical review of interventional, randomised, controlled trials, he attempted to answer the question of whether drug treatment of non-malignant hypertension reduces the incidence of renal dysfunction. He concluded that

"the relative risk (treated patients vs. controls) of developing renal dysfunction was 0.97 (95% confidence interval 0.78-1.21, p = 0.77) and that a 25% or more true protective effect of anti-hypertensive drugs is unlikely" and emphasized that the trials analyzed did not rigorously exclude patients with renal disease or reduced GFR, which would render more strength to his conclusion [15].

The previous considerations beg the question of what is the definition of hypertension-induced nephrosclerosis (HTN-NS) and its role as a cause of CKD. One should first consider that HTN-NS is recorded as the second most common causes of ESRD [21, 83]. It would appear that the diagnosis of hypertensive nephrosclerosis has replaced the previously used "chronic glomerulonephritis" to classify patients in whom a diagnosis for CKD is not apparent. Zarif *et al*. [84] showed that if strict clinical criteria are used, the prevalence of HTN-NS was reduced from 37% to less than 13% and possibly as low as 1.5%. However, as indicated by Marcantoni and Fogo [85], the strict clinical criteria of Schelesinger [86] which include a family history of hypertension, onset of hypertension between ages 25-45 years, target organ damage other than kidney (hypertensive retinopathy, left ventricular hypertrophy), no evidence of primary renal disease, minimal proteinuria and normal renal function, are not present in all patients with HTN-NS.

Clinical considerations: Clinicians should be aware of the difficulties of establishing a diagnosis of hypertensive renal disease. While biopsy confirmation is not always possible or even indicated, a specific notation of the clinical criteria upon which the diagnosis is based made should be made in the history. Since aggressive hypertension control with blood pressure target levels that reduce cardiovascular complications is a central therapeutic strategy in essential hypertension, is of little practical importance to determine if a higher blood pressure threshold is adequate for renal protection. Proteinuria and renal function should be closely followed. While inhibition of the angiotensin system is not mandatory in patients with uncomplicated essential hypertension, it should be strongly considered when renal functional deterioration or significant proteinuria are present.

The renal lesion resulting from hypertension

Two distinct morphological types of kidney injury result from hypertension and they may represent the ends of a spectrum of renal damage induced by increased blood pressure.

Malignant nephrosclerosis

The term malignant nephrosclerosis [87] is used to classify renal lesions associated with severe hypertension include proliferative endarteritis, fibrinoid necrosis with hyaline thrombi formation. The intimal hyperplasia results in concentric layers of collagen, designated with the term of onion skin. Prominence of the juxtaglomerular apparatus, interstitial inflammation and tubular atrophy may be present and vascular changes in the kidney correlate with the development of renal failure [7]. The natural (untreated) history of this type of injury is rapid progression to ESRD.

Nefrosclerosis

Typical lesions of HTN-NS include arterial medial thickening, hyaline deposits and variable intimal fibrosis. Glomerular lesions are segmental or global sclerosis. Since biopsies are not usually done to diagnose hypertensive nephrosclerosis the available studies on progression are usually retrospective and depend on a baseline clinical diagnosis. In studies by Fogo *et al*. that compared the agreement between the clinical and the pathological diagnosis [88] they found that concordance between the clinical and the biopsy diagnosis in hypertensive nephrosclerosis is high in Africa Americans but it occurs in only 48% of the Caucasian patients. Therefore the accuracy of the clinical diagnosis is related to genetic susceptibility of HTN-NS.

With the discussed limitations in mind, it is reasonable to suggest that non-malignant nephrosclerosis progress to ESRD, albeit at a significantly slower pace than its malignant counterpart [89-92].

Mechanisms of renal damage in hypertension

Figure 1 shows the interrelation between hemo-dynamic factors and humoral factors involved in the increment in extracelluar matrix in the renal damage induced by hypertension and the physiopathological mechanisms that are enga-ged by these factors.

Loss of autoregulation

Two decades ago, Brenner *et al.* [93] described the role of hyperfiltration and glomerular hypertension as a common final pathway in the progression of renal damage. Increased glomerular capillary hydraulic pressure [94] and glomerular hypertrophy [95] combine to compromise the resistance to physical stretch probably by modifying the structural support provided by the podocyte [96, 97] and in association with non-hemodynamic factors, cause glomerular sclerosis. The glomerular capillary pressure (P_{GC}) is the net result of the balance between the afferent and efferent arteriolar resistances and it may be increased in the absence of systemic hypertension in certain conditions like early diabetes, in which there is preglomerular vasodilatation and the reduction in afferent

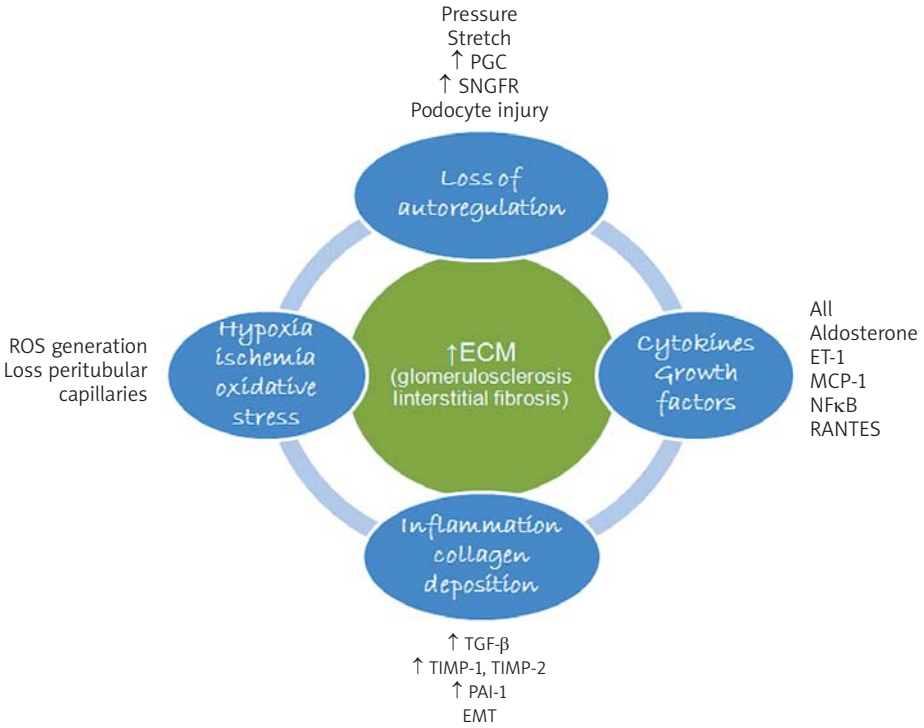

Figure 1. Hypertension-induced chronic renal damage
The increment in extracellular matrix (ECM) results from the interplay of hemodynamic factors and humoral factors as described in the text
PGC – glomerular capillary pressure, SNGFR – single nephron glomerular filtration rate, AII – angiotensin II, AT-1 – edotyhelin 1, MCP1 – macrophage chemotactic factor 1, NFκB – nuclear factor kappa B, TGF-β – transforming growth factorβ, PAI-1 – plasminogen activator inhibitor 1, EMT – epithelial mesenchymal transdifferentiation, ROS – reactive oxygen species

resistance exceeds the reduction in efferent arteriolar resistance. In relation to hypertension-induced renal damage, the glome-rular microvasculature is protected from systemic blood pressure increments by a phy-siological response of preglomerular asocon-striction that is proportional to the degree of hypertension.

Bidani and Griffin [98, 99] have elegantly described the pathophysiological consequences of hypertension in kidneys with preserved and impaired autoregulation. Patients with mild-to-moderate hypertension, who have preserved autoregulation of the glomerular blood flow, may withstand substantial increments in blood pressure without significant renal damage. In these circumstances the effects of a reduction in blood pressure (that was not in any case transmitted to the glomeruli) would not be expected to result in a proportional improvement in renal function. In contrast, if the blood pressure increments exceed the limits of the autoregulatory response, the renal damage occurs rapidly, as is the case in hypertensive crises, and the goal in treatment would be to lower the blood pressure to the range in which the autoregulation (assuming that is maintained within the physiological range in these patients) may offer protection to the glomerular vasculature. A different situation is that of experimental and clinical conditions in which impaired autoregulation is present. Such is the case in the late course of the experimental model renal ablation with extensive renal mass reduction and in diabetic nephropathy and in other nephropathies: In these circumstances there would be a linear relationship between the systemic blood pressure levels and the progression of renal damage and, consequently, the reduction of blood pressure is linearly related to the protection it may confer on the development of CKD. In these conditions, the lesser blood pressure the better protection. The adverse effects of impaired autoregulation are characteristic of conditions that have a vasodilated vascular bed; if the vascular bed is already vasoconstricted and autoregulation lost, the reduction of systemic blood pressure may result in a critical reduction of blood flow and glomerular filtration with ischemic downstream tubulointer-stitial injury [100].

The most impressive demonstration of the role of impaired autoregulation in the development of chronic renal damage has been obtained in

the model of 5/6 nephrectomy when blood pressure is evaluated by radiotelemetry. These studies showed a relationship between blood pressure levels and the progressive glomerulosclerosis [101, 102]. The administration of calcium channel blockers has adverse effects in this experimental model, with further reduction of the threshold in which blood pressure induces glomerulosclerosis; this finding has been attributed to the dependence of the autoregulatory vascular response on the voltage-gated calcium channels [103]. This characteristic may be responsable for the worse performance of calcium blockers in renal protection studies of diabetic nephropathy [71].

Herrera-Acosta *et al.*, in a series of investigations [104-106] demonstrated the role of tubulo-interstitial inflammation in the impairment of autoregulation of glomerular flow and thereby offered insight on the mechanisms linking tublointerstitial injury and glomerular sclerosis. As will be discussed later, when there is severe tubulointerstitial infla-mmation, a preglomerular arteriolar remodeling takes place, autoregulation is lost and there is a linear relationship between systemic and glomerular capillary pressure. If the tubu-lointerstitial inflammatory infiltrate is reduced by mycophenolate mofetil, the arteriolopathy and autoregulatory capacity of the glomerular circulation is restored. Interestingly, the admi-nistration of this drug ameliorates the renal disease progression in the renal ablation model [107, 108].

Cytokines and growth factors

The participation of non-hemodynamic factors involved in the renal injury resulting from hypertension was demonstrated by careful studies in which determinations of single nephron GFR, glomerular pressure and flow were investigated and the same micropunctured nephrons were identified and examined for histological changes at the time of sacrifice. In these studies [109], there was no correlation between the severity of glomerular sclerosis and the glomerular hemodynamic variables. In contrast, correlations were detected between gomerulosclerosis and glomerular hypertrophy several experimental models [110, 111]. Subsequently, Fogo [112] listed a number of human and animal models in which there was also an association between glomerular hypertrophy and sclerosis and reviewed how hypertrophic stimuli, such as high protein diet, high salt diet, growth hormone, insulin growth factor (IGF), androgens and glucocorticoids, promote renal hypertrophy and glomerular sclerosis and reviewed the therapeutic strategies that inhibit renal hypertrophy and meliorate glomerulosclerosis. In diabetes has long been recognized that increased renal and glomerular size precedes the development of sclerosis.

Renal hypertrophy is not only the result of increased work load since the glomerular hypertrophy precedes the increase in single nephron GFR in the remnant kidney model [113]. Growth factors and cytokines may be involved in the development of glomerular sclerosis associated with hypertrophy; among them, IGF, platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), Ang II, and interleukins (IL) may be involved in this pathologic response depending on the experimental model and the characteristics of the host [112]. Resident glomerular cells produce a large number of these compounds; notably vascular endothelial growth (VEGF), PDGF, nitric oxide (NO), endothelin and plasminogen activator-inhibitor 1 (PAI-1) by endothelial cells, and TGF-β, basic fibroblastic growth factor (bFGF) by mesangial cells. Increased matrix production by mesangial cells and structural dislocations in the podocyte structure contribute to the development of sclerosis. Modulation in the extracellular matrix turnover by PAI-1, epit-helial-mesenchymal transition by TGF-β and modification of proinflamatory/profibrotic genes involved in the sclerosis process and diabetic injury by peroxisome proliferator-activated receptor γ (PPAR-γ) [114] are likely involved in the very complex mechanisms triggered and sustained by growth factors and cytokines in hypertensive chronic renal damage.

Renal hypoxia

Chronic hypoxia is a mechanism for the development of chronic renal damage [115] that is likely engaged in hypertension. Chronic tubulointerstitial hypoxia is the result of several factors present in hypertensive nephropathy. Among them, a reduction in blood flow to nephrons in regions distal to obsolescent glomeruli, an imbalance of vasoactive substances in favor of vasoconstriction resulting from interstitial inflammation and the loss of peritubular capillaries associated with the development of fibrosis. Superoxide production induced by Ang II is known to result in proinflammatory and profibrogenic mediators, as will be discussed later. Not unexpectedly, blockade of the RAS improves peritubular capillary blood flow and tissue oxygenation in healthy rats [116] and in the remnant kidney [117]. The effects of hypoxia and oxidative stress may be present in an early stage in the kidney in conditions such as diabetes that later develop hypertension and structural kidney damage, as has been demonstrated streptozotocin-induced diabetes with blood oxygen level dependent (BOLD)-magnetic resonance imaging [118].

Another effect resulting from increased oxidative stress is the decrease in NO availability which is a protective factor of vessel integrity and antagonizes Ang II hemodynamic [119] and non-hemodynamic effects [120]. Reduction in NO facilitates vascular remodeling [121] which promotes tissue ischemia.

Renal angiotensin system

The renal RAS plays an important role in the hypertension-induced chronic renal damage. It is important to realize that all the components of the RAS are present in the kidney [122] and its activity is not modulated by the same influences that modify plasma Ang II levels; for instance plasma expansion reduces plasma AII levels but does not modify RAS [123, 124]. Furthermore, in salt-sensitive hypertension the severity of hypertension is negatively correlated with plasma AII levels and positively correlated with renal AII levels [125].

Increased renal Ang II has been demonstrated in all experimental models of salt sensitive hypertension. Proximal tubular cells as well as infiltrating cells express Ang II [126-130] and the renal content [131, 132] and the interstitial concentration of AII are increased in association with renal inflammation in experimental hypertension [125, 133].

Angiotensin II induces oxidative stress. Generation of superoxide by NAD(P)H oxidase is stimulated by AII via angiotensin type I receptors [134-136]. Angiotensin is also a well recognized factor in the inflammatory and profibrotic effects of hypertension [137] and its effects are in large measure mediated by the stimulation of the proinflammatory transcription such as nuclear factor kappa B (NFκB) which is a central mechanism in the stimulation of the angiotensin-induced cytokine stimulation [138, 139], possibly including the downstream stimulation of connective tissue growth factor [140]. In addition, as recently shown by Carvajal *et al*. [141], Ang II activates the Smad pathway during the profibrotic process of epithelial mesenchymal trans differentiation. Given the key role that is played by angiotensin in the proinflammatory and profibrotic damage in the kidney, is not unexpected that inhibition of the renal angiotensin system by ACE inibitors and ARBs hypertensive renal damage as discussed earlier.

Aldosterone

Hyperaldosteronism is present in the renal remnant model in association with renal failure, hypertension, proteinuria and nephrosclerosis. Since the administration of exogenous aldosterone in rats with renal ablation treated with angiotensin blockers reinstated the renal damage [142], there appears to be a pathogenetic role of aldosterone in this model. However the beneficial effects of aldosterone blockade on the remnant kidney are relatively modest [143].

Aldosterone participation in the renal damage induced by hypertension may result from its ability to stimulate synthesis of sodium channels and increased influx of sodium in vascular smooth muscle cells (VSMC) [144] and by promoting hypertrophy of these cells by enhancing AII receptor binding [145]. In addition, aldosterone inhibits NO synthesis [146].

Aldosterone induces post-transcriptional enhancement of TGF-β [147], an effect that likely explains the manner in which aldosterone antagonism results in reduction of collagen content independently of the blood pressure levels [148, 149].

While the clinical studies of the potentially independent beneficial effects of aldosterone blockade are related to endothelial dysfunction and heart failure [150-152], in stroke-prone hypertensive rats, aldosterone antagonists reduces proteinuria and nephrosclerosis [153] independently of changes in blood pressure [154].

The effects of aldosterone promoting chronic renal damage are likely mediated by intrarenal inflammation since the beneficial effects of aldosterone aldosterone blockade in the mineralocoricoid/salt hypertension is associated with a reduction of the inflammatory reactivity [155].

Intrarenal inflammation

Renal inflammation plays a role in all modalities of progressive renal damage [156] and CKD resulting from hypertension is no exception. In all the experimental models in which it has been tested, the reduction in the tubulointerstitial infiltration of imunocompetent cells is associated with an amelioration of hypertension or prevention of the salt-induced increment in blood pressure [78]. The renal inflammatory reactivity is closely linked with both oxidative stress and with intrarenal angiotensin system [157]. Infiltrating cells generate reactive oxygen species and, in turn, oxidative stress and superoxide estimulate the proinflammatory transcription factors, most notably NFκB [158], thereby promoting further local inflammatory reactivity. As discussed earlier, Ang II generates superoxide and directly stimulates NFκB. The inflammatory infiltration increases local Ang II, as shown by an increment in the number of cells expressing AII [126-128] and the increment in renal content and interstitial fluid concentration of AII which is reduced by the immunosuppressive anti-inflammatory treatment [125, 131, 132].

The reduction in tubulointerstitial inflammation has been shown to reduce or prevent the afferent arteriolar remodeling that is present in experimental models of hypertension [104-106]. The prevention of arteriolar remodeling is important because the remodeling of glomerular arterioles impairs the autoregulatory responses of afferent arterioles which, as described earlier, are critical to protect the glomerular capillaries from the pressure and stretch modifications that otherwise result from elevations of systemic blood pressure.

Proteinuria

Proteinuria is a risk factor and a marker of CKD and one of the most important elements to control in any strategy designed to retard progression of renal damage. As discussed earlier, the beneficial effects of RAS inhibition are more, and perhaps only evident in patients with important proteinuria in whom treatment with ACEi, ARBs or both result in a reduction in urinary protein excretion. However, proteinuria is probably of minor importance in hypertensive nephropathy. In fact, the absence of significant proteinuria is an important clinical characteristic of essential hypertension. Microalbuminuria (20-200 mg/day) has been proposed as a marker of generalized endothelial dysfunction and is present in probably 15% of the patients with essential hypertension but the prognostic significance of this finding in this patients is unknown at the present time [87].

Dislipidemia in the pathophisiology of chronic kidney disease

An association between lipid abnormalities and the pathogenesis of kidney disease was first suggested by Virchow in 1860 when he described extensive fatty deposits in renal tissue obtained by autopsy in a patient with Bright's disease [159]. Chronic kidney disease results in profound lipid disorders, which derive largely from dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism [160]. Characteristically, a moderate increase in apo B-containing lipoproteins of very low and low densities, and reduced levels and abnormal composition of apolipoprotein A-containing lipoproteins (Apo A) of high densities are present. Additionally, triglyceride enrichment of apo B-containing lipids (Apo B) is an important abnormality that correlates with progression of kidney disease. The presence of small dense, triglyceride-enriched particles associated with reduced high density lipoprotein is also a major risk factor involved in cardiovascular disease [161-163]. In both, type 1 and type 2 diabetes, the dyslipidemia is not just secondary to kidney disease, since an unfavorable lipid profile is present at early stages of microalbuminuria. Higher levels of plasma triglycerides, lower plasma HDL-cholesterol are found in hypertensive diabetic patients with increased sodium-lithium countertransport when GFR is normal [164].

Two primary lipid disorders have been associated with renal disease. Patients with a deficiency of lecithin-cholesterol acetyltransferase (LCAT) develop large lipid-laden lipoproteins, glomerular lipid deposits and eventually renal failure associated with glomerulosclerosis. Abnormalities in apolipoprotein E-containing lipoproteins (Apo E) have been described with a distinct form of progressive kidney disease characterized by proteinuria, type III hyperlipoproteinemia, lipoprotein thrombi in glomeruli, and an apolipoprotein E variant, named ApoE Sendai. (165, 166). The functions of Apo E phenotypes are considered relevant not only to the pathogenesis of hyperlipidemia and glomerular disease, but also to atherosclerosis [167].

The following section, will be focused on the association between the lipid profile and the progression of CKD, mechanisms of dyslipidemia-induced renal damage and lipid disorders resulting from renal disease and the effects of statins on renal disease progression.

Association between plasma lipid profile and progression of chronic kidney disease

It has been suggested that the renal dyslipoproteinemia of renal insufficiency contributes to the progression of glomerular and tubular lesions [160, 161, 168]. Samuelsson *et al*. [169] reported that in a study of 73 adult non-diabetic patients with primary chronic renal disease, total cholesterol, low-density lipoprotein (LDL) cholesterol, and Apo B were associated with a more rapid decline of in renal function. Subsequently, in a separate study, the same group described a strong association between the plasma concentration of complex, triglyceride-rich Apo B-containing lipoproteins and the rate of progression of kidney disease [170]. Also, in the study of Hovind *et al*. [171], in 92 (31%) out of 301 patients with nephropathy associated with type 1 diabetes, remission was associated to a lower serum cholesterol, mean arterial pressure, and albuminuria.

Similar associations between dyslipidemia and CKD were found in a *post hoc* analysis of the Reductions of End Points in type 2 Diabetes with the Angiotensin II antagonist Losartan RENAAL study, that reported that increased total cholesterol, LDL cholesterol, and triglycerides were associated with increased risk of progression to ends stage kidney disease [172].

In an study of risk factors for diabetic nephropathy in 574 patients type 2 diabetes mellitus, multiple logistic regression analysis indicated that levels of total cholesterol, were among the main

factors associated with the decreased in renal function and with the increase of albuminuria [173]. In addition, it also has been shown that patients with low HDL and hypertriglyceridemia have a higher risk of having a loss of renal function [174]. Similarly, low HDL cholesterol was found an independent predictor of a decline in GFR in patients with kidney disease, although triglycerides levels were not measured [168]. Hipertryglyceridemia has also been identified as an independent risk factor for progression of IgA nephropathy [175].

Apo E genetic variation has been implicated in diabetic nephropathy. In a prospective follow-up of the Atherosclerosis Risk in Communities (ARIC), the ε2 allele increased and ε4 decreased risk of CKD progression independently of age, gender and race [176]. The ε2 allele has been associated with type III hyperlipoproteinemia and increased levels of triglycerides due to delayed clearance, both associated with kidney disease [177]. This finding has not been confirmed by others investigators [178].

Unexpectedly, it has recently been reported the association of a higher apoA-IV levels with progression of kidney disease [178]. Normally, apoA-IV removes cholesterol from peripheral cells and directs it to the liver for metabolism. Furthermore, apoA-IV has antioxidative properties, and therefore should slower progression of CKD. The authors suggested that perhaps apoA-IV is not fully functional or that high levels reflect an aspect of renal dysfunction that is not reflected in reduction in GFR.

Finally, others researchers have found no relation of dyslipidemia and progression of kidney disease [179, 180]. Size of the sampled population, differences in inclusion criteria or in the definition of the progression end point might explain these discrepancies.

Mechanisms of dyslipidemia-induced renal damage

Dyslipidemia-induced oxidative stress

Several lines of evidence indicate that oxidant stress is a pathogenic factor in lipid induced kidney disease. The presence of lipoproteins modified by oxidation has been demonstrated in focal segmental glomerulosclerosis in rats and humans. Lee *et al.* [181] have demonstrated that rats with focal segmental glomerulosclerosis and dietary hypercholesterolemia showed significantly greater susceptibility of plasma very-low density lipoprotein (VLDL) and LDL to in vitro oxidation and increased renal cortical malondialdehyde (MDA), suggesting that hypercholesterolemia could make lipoproteins more susceptible to oxidation. These findings have also been documented by others [182]. Lee and Kim [183] demonstrated that oxidized-LDL (ox-LDL) is present in human kidney biopsies in mesangial areas and in the lesions of glomerulosclerosis. The presence of ox-LDL and oxidized-Lp (a) contribute to inflammation by stimulating O_2^- formation, and induce apoptotic cell death in the vascular wall and in the glomerulus [184].

The mechanisms leading to oxidative modification of proteins and lipoproteins have not been entirely elucidated. Scheuer *et al.* [185] have suggested that the increased generation of reactive oxygen species (ROS) is primarily the result from an elevated xanthine oxidase activity. In their study, hyperlipidemia was induced in uninephrectomized rats without preexisting glomerular disease and in those with mesangioproliferative glomerulonephritis. Hyperlipidemia resulted in a rise in glomerular and tubulointersticial generation of ROS. Oxygen radicals were mainly generated by enhanced xanthine oxidoreductase, which rose during hyperlipidemia; concurrently, glomerulosclerosis and chronic tubular interstitial injury were associated with hyperlipidemia which also accelerated tubulointerstitial injury in rats with glomerulonephritis.

Triglyceride-rich lipoproteins, LDL, and ox-LDL may induce mesangial cell proliferation and injury in patients with mesangial proliferative glomerulonephritis. Nishida *et al.* [186] have reported that VLDL, intermediate-density lipoprotein (IDL) and LDL induced the proliferation of cultured human mesangial cells and enhanced the production of IL-6, PDGF-AB and TGF-β while tumour necrosis factor α (TNF-α) secretion was stimulated by oxidized LDL [187]. The mechanisms involved in cell proliferation induced by accumulation of LDL and its oxidized forms include activation of membrane receptors of the Ras and mitogen-activated protein (MAP) kinase signaling cascades leading to increased DNA synthesis [188].

Dyslipidemia and endothelium-derived vasodilators/growth inhibitors

Increased LDL cholesterol is associated with impaired NO-mediated vasodilation. Available data suggest that reduced NO availability in dyslipidemia is due to increased degradation of NO rather than decreased production. Inhibition of endothelial relaxation induced by oxidized LDL cholesterol may be due to the formation of lysophosphatidylcholine (lyso-PC), derived from the oxidation of LDL [189].

Dyslipidemia and macrophage infiltration and activation

A number of studies have demonstrated an important role for macrophages in the development of glomerular injury. The mechanisms whereby dyslipidemia facilitates monocyte recruitment to the glomeruli are incompletely understood but may

involve the increased production of chemokynes and upregulation of adhesion molecules. Lovastatin reduces expression and production of monocyte chemoattractant protein-1 (MCP-1) and macrophage-colony stimulating factor (M-CSF) in cultured mesangial cells [190]. Hattori *et al*. [191] demonstrated an infiltration of macrophages-derived foam cells in almost all the glomeruli in rats fed a high cholesterol diet. Many of these cells expressed of lymphocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4), which are ligands for intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1). Coincident with the induction of hypercholesterolemia, a marked up-regulation of Mo colony-stimulating factor (M-CSF) and Mo migration inhibitory factor (MIF) mRNA was expressed by glomerular mesangial cells and podocytes. These authors [191] concluded that hypercholesterolemia can induce a classic proinflammatory response which results in macrophage recruitment and glomerular injury. Consistent with these investigations, the ApoE null mice, a model of hypercholesterolemia, fed with a high cholesterol diet, develope mesangial expansion in association with a glomerular inflammatory response characterized by the presence of foam cells, macrophage recruitment, and endothelial-cell activation [192]. These findings were not aggravated after subtotal nephrectomy and were therefore independent of renal mass reduction [193].

In summary, the presence of ox-LDL in the glomeruli may recruit circulating monocytes, leading to the accumulation of macrophages in the glomeruli. Activated macrophages secrete cytokines, growth factors, vasoactive substantances, coagulation factors, reactive oxygen species, and proteolytic enzymes, leading to glomerulosclerosis by augmenting mesangial cell proliferation. In addition, macrophages have a large number of scavenger receptors and accumulate oxidazied LDL within cells, resulting in foam cell formation. When these cells die, the release of cytotoxic components could cause a loss of glomerular cells and lead to an eventual sclerosis of the glomeruli, as proposed in atherogenesis (Figure 2) [181-193].

Dyslipidemia induced by renal disease

Upregulation of 3-hydroxy-3-methylglutaryl CoA reductase

The nephrotic syndrome is associated with multiple derangements in lipid metabolism. Vaziri *et al*. [194, 195] have demonstrated a marked

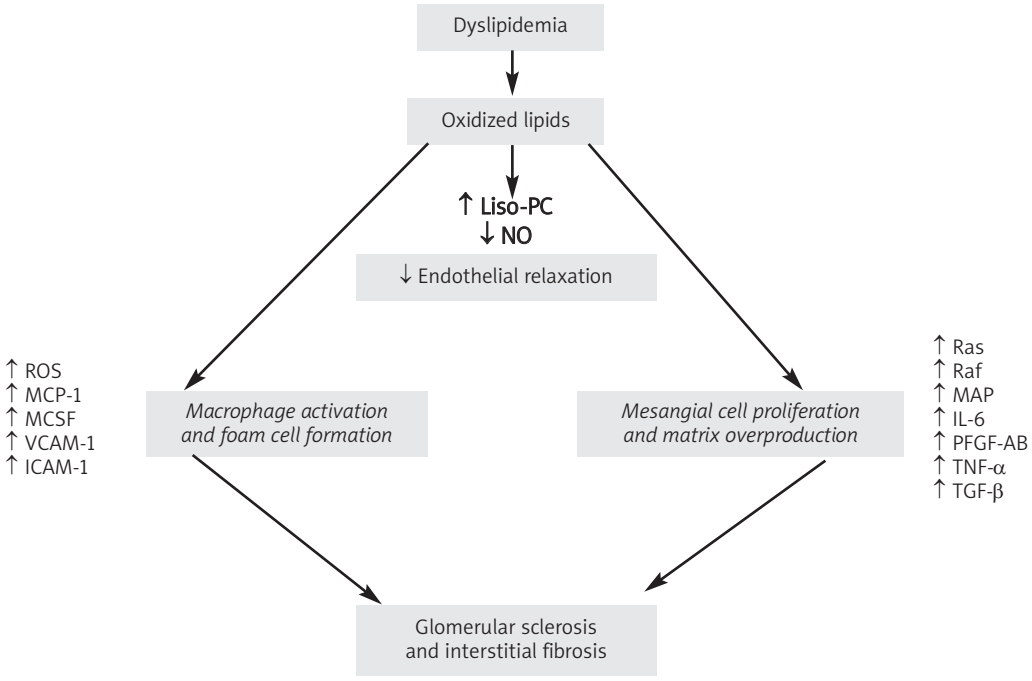

Figure 2. Lipid-induced chronic kidney disease
The presence of oxidized lipids in the glomeruli results in glomerular sclerosis by the interplay of macrophage activation, mesangial cell proliferation and an imbalance of the vasoconstriction/vasodilatation mechanisms
NO – nitric oxide, Liso-PC – lysophosphatidylcholine, ROS – reactive oxygen species, MCP1 – macrophage chemotatic factor 1, MCSF – macrophage-colony stimulating factor, ICAM-1 – intercellular adhesion molecule-1, VCAM-1 – vascular adhesion molecule-1, Ras – Ras proteins, MAP – mitogen-activated protein, IL-6 – interleukin-6, PDGF-AB – platelet-derived growth factor-AB, TNF-α – tumor necrosis factor α, TGF-β – transforming growth factor β

upregulation of 3-hydroxy-3-methyl-glutaryl CoA reductase (HMG-CoA reductase) and a relative reduction of hepatic cholesterol 7 α-hydro-xylase (Ch 7 α-hydroxylase). These alterations are accompanied by LDL receptor deficiency, and up-regulation of hepatic ACAT-2. These molecular disregulations are responsible for the induction and maintenance of hypercholesterolemia, impaired LDL clearance and cholesterol enrichment of VLDL and newly synthesized LDL particles in patients with the nephrotic syndrome [194, 195].

Lecitin-cholesterol acetyltransferase deficiency

Lecitin-cholesterol acetyltransferase is a glycoprotein enzyme that is synthesized by the liver and secreted in plasma where it catalyzes the removal of the fatty acyl group from the sn-2 position of lecithin and its transfer to free cholesterol to form cholesteryl ester. Inherited LCAT deficiency is associated with a marked reduction in HDL-mediated reverse cholesterol transport, a depressed ratio of cholesterol-rich HDL2 to cholesterol-poor HDL3, the presence of cholesterol laden foam cells in various tissues, accelerated cardiovascular disease, corneal opacification, and progressive renal disease [196].

The animal model of LCAT deficiency (LCAT-KO mice) develops a clinical phenotype similar to humans. In addition to severe alpha-lipoproteinemia, LCAT-KO mice present with normochromic normocytic anemia and glomeruloscerosis. The findings indicate that the induction of lipoprotein X (LPx) by a high fat-high cholesterol diet is associated with the development of glomerulosclerosis in these mice [197]. In the nephrotic syndrome, hyperlipidemia is marked by elevations of plasma LDL, VLDL, IDL, and lipoprotein (a) [194]. Although HDL levels are generally normal, the maturation of HDL_3 to HDL_2 is impaired, due to acquired LCAT deficiency secondary to abnormal urinary losses of this enzyme [198].

Downregulation of lipoprotein lipase activity

Lipoprotein lipase (LPL) is the rate-limiting step in lipolysis of VLDL and chylomicrons. The down regulation of LPL activity results in their impaired clearance and is responsible for the elevation of serum triglyceride concentration. The studies of Liang and Vaziri [199] in nephrotic rats have demonstrated marked downregulation of LPL in skeletal muscle, myocardium, and adipose tissue, the principal sites of consumption of fatty acids. The reduction in LPL activity plays a role in the pathogenesis of hyperlipidemia and thereby in the increased risk of progression of kidney and cardiovascular disease.

The statins role in the progression of chronic kidney disease

Lipid-lowering and anti-iniflammatory effects

Statins, due to their hypolipidemic effect are useful in correcting the dislipidemia of patients with CKD and reducing cardiovascular events in this population. In addition, several studies have suggested that the HMG-CoA reductase inhibition, may have additional effects on the biology of inflammation involved in the progression of kidney disease. It is now widely accepted that HMG-CoA reductase blockade not only inhibits the synthesis of cholesterol but also the mavelonate pathways and the synthesis of isoprenoids, such as farnesyl pyrophosphate (FPP) and geranyl geranyl pyrophosphate (GGPP). Isoprenoids are essential for the posttranslational modification of several proteins involved in important signaling pathways [200, 201].

Statins may exert their protective effects on renal disease progression through a variety of immunomodulatory effects, down regulation of proinflammatory and profibrotic cytokines and antiproliferative effects on smooth muscle cells and mesangial cells. Immunomodulatory effects are exerted through modification of multiple proinflammatory transcription factors, such as NFκB, signal transducer of transcription 1 (STAT-1), hypoxia-infucible factor (HIF), peroxisome proliferators-activated receptors α (PPAR-α), and kruppel-like factor 2 (KLF2) [202]. In rats with subtotal nephrectomy, atorvastatin appears to confer nephroprotection as a result of down regulation of prosclerotic cytokines such as TGF-β_1 and reduced macrophage accumulation [203]. Treatment with lovastatin in diabetic rats inhibited TGF-β_1 mRNA expression in diabetic rat glomeruli and cultured rat mesangial cells despite high glucose levels. These changes were nearly completely restored by mevalonate [204].

The statins could affect the smooth muscle cells proliferation through inhibition of the isoprenylation of small GTP binding proteins Rho or Rac. Through modification of these two proteins, statins have been shown to inhibit VSMC proliferation by arresting the cell cycle between the G1/S phase transition [202]. In addition, inhibition of protein prenylation by statins may play a role in VSMC apoptosis, providing another mechanism by which HMG-CoA reductase inhibitors may modify the pathophysiology of vascular sclerosis [205].

Many glomerular diseases are characterized by mesangial cell proliferation and accumulation of mesangial extracellular matrix. Treatment with lovastatin reduced mesangial cellularity in obese Zucker rats, Dahl salt-sensitve rats and rats with subtotal nephrectomy [206, 207]. Initially, these

effects were attributed to the lipid-lowering effect of lovastatin; subsequently, it was demonstrated that lovastatin prevents cell proliferation via a dose-dependent reduction of DNA synthesis. This effect was largely abrogated by mevolonate and isoprenoid farnesol [208]. Simvastatin suppressed cell mesangial proliferation and subsequent matrix expansion, and glomerular macrophage infiltration in the Thy-1 rat model of glomerulonephritis. The effect of simvastatin was also associated with the reduction of the cyclin dependent kinase 2 (CDK2) in mesangial cells [209], an enzyme regulates cell proliferation [210]. Lovastatin can also decrease PDGF-induced mesangial cell DNA synthesis and cell membrane Ras incorporation, a mechanism involved in the pathogenesis of proliferative glomerular disease [211].

In cultured mesangial cells, pravastatin inhibits inflammatory mediators, macrophage infiltration, and suppresses mesangial cell proliferation, TGF-β_1 expression, and extracellular matrix production (fibronectin and type IV collagen) [212] and type IV collagen production, DNA synthesis and G1 to S phase progression [213]. In a rat model of chronic cyclosporine-induced nephropathy, pravastatin induced dose-dependent decreases in the expression of osteopontin and intrarenal C-reactive protein, of fibrotic cytokine-TGF-β_1 and in the numbers of infiltrating macrophages. In addition, Pravastatin also upregulated the endothelial nitric oxide synthase (eNOS). These changes were accompanied by a significant attenuation of tubulointerstitial inflammation and fibrosis [212]. In salt-loaded Dahl salt-sensitive rats, pravastatin ameliorated the renal oxidative stress, and retarded the progression of kidney injury [214].

HMG-CoA reductase inhibition can prevent interstitial fibrosis. In an experiment where proximal tubules isolated from rats were treated previously with lovastatin, it was observed an increase of tissue-type plasminogen activator (tPA) and urokinase (uPA) activities. These effects were also observed when proximal tubules from untreated rats were incubated with lovastatin. *In vitro*, supernatants, cytosols, and membranes of proximal tubular cells showed the same effects when exposed to lovastatin. These effects were reversed by mevalonate and GGPP but not by FPP. The effect of lovastatin was associated with a disruption of cellular actin stress fibers, which was reversed by GGPP. The resulting increase of proteolytic activity of tubular cells may downregulate extracellular matrix deposition [215]. Similar results have been reported with the use of rosuvastatin [216].

Another mechanism whereby statins could prevent interstitial fibrosis is by reducing protein tubular absorption and decreasing intraparenchymal protein trafficking. Renal proximal tubule cells are responsible for the reabsorption of proteins that are present in the tubular lumen by a process that involves receptor-mediated endocytosis. Statins inhibited the uptake of albumin by the proximal tubule-derived opossum kidney cell line and the reduction in albumin uptake was related to the degree of inhibition of HMG-CoA reductase [217]. The effect on albumin endocytosis was prevented by mevalonate and by the isoprenoid GGPP, indicating that the inhibitory effect may be caused by reduced prenylation and thereby decreased function of GTP-binding proteins required for this process [217, 218]. This mechanism could also be involved in the proteinuria observed in patients treated with a high dose statins [219].

In summary, a wide range of effects have been reported with statins, including antinflammatory and immunomodulatory effects, mesangial cell proliferation and reduction of albumin uptake by the proximal tubule cells. They all are independent of their lipid-lowering effect, and they could represent additional mechanisms for the renoprotective effects of statins.

Clinical evidences

Results from several small clinical studies initially suggested that statins might slow the progression of kidney disease [220]. Subsequently, the sub-analyses of large randomized trials have reported that statins may slow renal function loss in CKD. In a post hoc analysis from the Cholesterol and Recurrent Events (CARE) trial, a randomized study of pravastatin vs. placebo, data from a subset of participants with moderate chronic renal disease (estimated GFR < 60 ml/min/1.73 m^2) was analyzed. In this subgroup of patients, the rate of GFR decline the pravastatin-treated patients was slower than in those treated with placebo. This effect was more pronounced in individuals with proteinuria at the baseline [221]. However, the same authors reported in a subsequent meta-analysis that a modest reduction in proteinuria and a small reduction of the kidney functional loss, was found mostly in individuals with cardiovascular diseases [222].

In a subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation study (GREACE), the effects of statins vs. untreated dyslipidemia was evaluated. In untreated dyslipidemic patients with coronary heart disease (CHD) and normal renal function at baseline, renal function declined over a period of three years. Statins treatment prevented this decline and significantly improved renal function [223]. The subanalysis of the Treating to New Targets (TNT) study compared 80 mg of atorvastatin with 10 mg of the drug in the renal function of patients with CHD. At the end of a mean of 59.5 months of follow-up,

the expected decline in renal function was not observed and GFR improvement was significantly greater with the higher dose (224). The renoprotective effect of statins may be enhanced when combined with ACEi inhibitors or ARB treatment. In a prospective, controlled, open-label study, treatment with atorvastatin added to a regimen with ACEi inhibitors or ARB, reduced significantly the rate of progression of kidney disease and proteinuria in patients with CKD [225]. Similar findings have been reported in experimental nephropathy [226].

In contrast, other studies have not confirmed that statins retard the progression of CKD. In a post hoc subanalysis of the Antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT), pravastatin was not superior to usual care in preventing clinical renal outcomes in hypertensive patients with moderate dyslipidemia and decreased GFR [227]. It has been argued that the negative results of this analysis might be due to the unique design of this trial [228].

In conclusion, there are potential mechanistic explanations to justify the use of statins to slow the loss or renal function and proteinuria in patients with CKD. However, the available clinical data is inconclusive to determine if statins retard the progression of kidney disease. Most of the studies come from a post hoc analysis of large clinical trials not intended to evaluate primarily the effect of statins on kidney function.

Therefore, at the present time the decision to use statins in the context of slowing kidney disease progression is left to the physician judgment.

Acknowledgments

Research in BRI laboratories is supported by FONACIT grant F-2005000283, Ministerio de Ciencia y Tecnología, Venezuela and Grant in Aid from the Asociación de Amigos del Riñón, Maracaibo, Venezuela. Research in GG laboratories is supported by Fundación Hospitales Civiles de Guadalajaray Registro de Diálisis y Trasplante del Estado de Jalisco, Mexico.

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