

# NEPHROPROTECTION, PART OF MULTI-ORGAN PROTECTION

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## REZUMAT

Nefroprotecția, care în ultimul timp a cunoscut o amplă dezvoltare, include totalitatea măsurilor care se adresează rinichiului, protejându-l împotriva factorilor agresivi. Rinichiul, creierul și cordul pot fi afectate concomitent în diverse circumstanțe. Toate organele amintite prezintă o vascularizație bogată, din acest motiv factorii îndreptați împotriva vascularizației vor duce la o agresiune concomitentă a rinichiului, cordului și creierului. Principalii factori agresivi îndreptați împotriva rinichiului și care afectează concomitent inima și creierul sunt reprezentați de hipertensiunea arterială, sistemul renină-angiotensină-aldosteron, afectarea metabolismului lipidic, rezultând ateroscleroza, creșterea aportului de sare, tulburări ale metabolismului glucidic, cum ar fi diabetul zaharat sau alte tulburări metabolice, perturbările echilibrului acido-bazic, stresul oxidativ și anemia. Organismul este afectat în totalitate în timpul acestor perturbări. Un pacient cu boală cronică de rinichi poate prezenta leziuni ale multor organe necesitând măsuri nefroprotective pentru leziunile renale, asociate cu măsuri cardioprotective pentru leziunile cardiace și măsuri neuroprotective pentru leziuni ale sistemului nervos. Măsurile protective de organ incluse în nefro, cardio și neuroprotecție, la fel ca și măsurile de protecție celulară și moleculară, se suprapun. Ele păstrează specificitatea de organ, dar în același timp majoritatea dintre ele cuprind patologia regională, determinând multiorganprotecția. Boala cronică de rinichi reprezintă o componentă importantă a bolilor cardiovasculare și neurologice și nu numai, ce impune de asemenea atât măsuri de nefroprotecție, cât și de neuroprotecție și cardioprocție, respectiv multiorganprotecție. Unele măsuri protective de organ acționează și asupra altor organe, de exemplu inhibitorii de enzimă de conversie (IECA) au acțiune renoprotectivă dar în același timp prezintă acțiuni cardio și neuroprotective. În acest caz măsurile organprotective se transformă în multiorganprotecție. Nefroprotecția reprezintă o componentă a multiorganprotecției, ea beneficiind de măsurile terapeutice multiorganprotective, iar în același timp medicația renoprotectivă are valențe de multiorganprotecție.

**Cuvinte cheie:** nefroprotecție, multiorganprotecție, IECA, boală cronică renală, homocisteină, inflamație, statine

## ABSTRACT

Nephroprotection has known ample development lately and consists in the measures which protect the kidney against many aggressive factors. The kidney, the brain and the heart can all be affected concomitantly under several circumstances. All of them have a rich blood supply, and the aggressive factors that influence it will concomitantly affect the kidney, the heart and the brain. The main factors targeting the kidney, concomitantly affecting the heart and the brain are: arterial hypertension (AHT), the renin-angiotensin-aldosterone system, lipid profile alterations with subsequent atherosclerosis, homocysteine, increased salt intake, carbohydrate metabolism disorders like diabetes mellitus and other metabolic disturbances, disorders of acid-base balance, oxidative stress and anemia. The body is affected in its entirety by these factors. A patient with chronic kidney disease (CKD) can present with multiorgan injuries that need to be addressed, thus imposing nephroprotective measures aimed at the renal lesion, associated with cardioprotective measures for the cardiac lesion and neuroprotective measures for the lesion of the nervous system. Organ-protective measures entailed in nephro-, cardio- and neuroprotection, as well as measures of cyto- and molecular protection overlap. They keep the specificity of the organ, but at the same time, most of them outstretch the domain of regional pathology, defining multiorgan protection. Chronic kidney disease represents an important component of cardiovascular and neurological diseases that require apart from neuro- and cardioprotective measures also nephroprotective measures, multiorgan protection respectively. Some organ-protective measures exhibit protective actions on other organs, too. Angiotensin conversion enzyme (ACE) inhibitors, for example, have a renal protective action, but at the same time they have also cardiac and cerebral protective actions. In this case nephro-protective measures are encompassed in the broader frame of multiple organ protection. Nephroprotection represents a component of multiorgan protection demanding multiorgan protective measures, and at the same time renoprotective drugs with multiorgan protective properties.

Key words: nephroprotection, multiorgan protection, ACE inhibitors, chronic kidney disease, homocysteine, inflammation, statins

## INTRODUCTION

A patient with a chronic disease can show injury of many organs that need to be addressed. A patient with

diabetes mellitus needs nephroprotective measures against the renal lesion, cardioprotective measures for the cardiac lesion and neuroprotective measures for the lesion of the nervous system. Treatment consists in organ-protective therapy, as well as protective measures that are aimed at correcting multiple organ dysfunctions concomitantly.

We will subsequently use the terms nephroprotection, cardioprotection and neuroprotection in regard with organ-specific measures, while when these protective measures are targeted against many organs we will use the term of multiorgan protection.<sup>1</sup>

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Organ-protective measures focus on a single organ, such as nephroprotective, cardioprotective or neuroprotective measures. Some organ-protective measures exhibit protective actions on other organs, too. ACE inhibitors, for example, have a renal protective action, but at the same time they also have cardiac and cerebral protective actions. In this case organ-protective measures cross into to the field of multiple organ or multi-organ protection.

The issue is to establish the common features of the kidney, the brain and the heart, in order to explain the similar lesions that impose common therapeutic protective measures. The circulatory system, with the heart and major blood vessels at its center will ensure blood flow to the periphery, including heart, kidney and brain. The heart depends on the coronary vessels to allow an adequate functioning. The brain has a well represented blood supply, which can not adapt to hypoxia, and the renal blood flow represents approximately 20% of the circulating volume. Consequently different alterations of the circulatory system will impact on these organs. For example, hypertension concomitantly affects kidney, heart and brain. The use of ACE inhibitors and AII

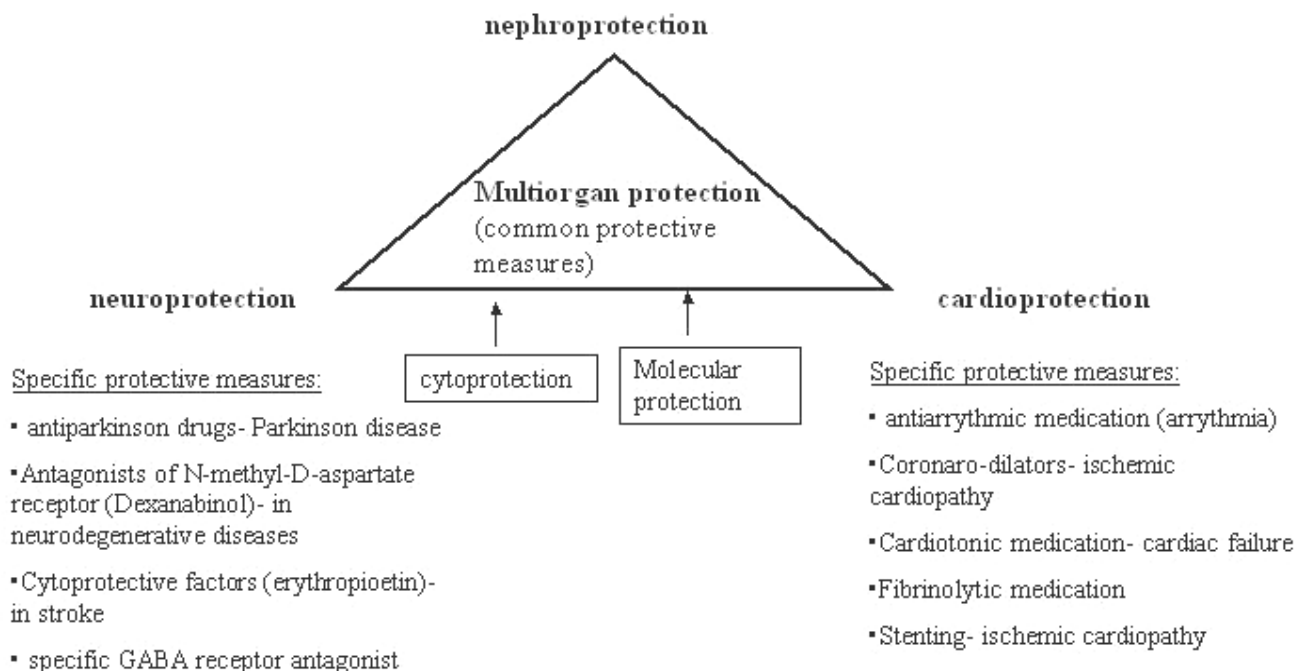
receptor blockers will have a complex nephro-, cardio- and neuroprotective effect. Lesions secondary to atherosclerosis, as well as inflammatory diseases will have an effect on the vascular endothelium. The use of statins will influence the lipid profile and consequently the effect of the latter on coronary, renal and cerebral blood flow. Diet will have similar effects. Likewise, sulodexide exerts a protective effect on the vascular endothelium by correcting glycosaminoglycans.

Glucose metabolism changes will also influence the body as a whole. They are reflected metabolically or hemodinamically by means of secondary alterations of lipid metabolism. The approach of glucose metabolism will have consequences on kidney, heart and brain.

Hypoxia secondary to anemia that accompanies advanced chronic kidney disease concomitantly afflicts the heart. Silverberg describes a triad: anemia, chronic kidney disease and heart disease, with overlapping pathology.<sup>2</sup> Hypoxia also affects the brain producing functional alterations at this level. Correction of anemia of chronic kidney disease through nephroprotective measures which consist of iron, folic acid and erythropoietin will have consequences

Specific protective measures:

- proteinuria (NSAIDs, corticotherapy)
- Anaemia- insufficient erythropoietin secretion- erythropoietin
- Phospho-calcic disorders- phosphate absorption inhibitors (Calcium carbonate, sevelamer, calcimimetics)
- Chronic inflammation, uraemic toxins- renal replacement therapies



**Figure 1.** Nephroprotection - component of multiorgan protection, in relationship with cardioprotection, neuroprotection, cytoprotection and molecular protection.

on the kidney by improving the reduced production of erythropoietin and its function, but will also impact the heart, by improving cardiac disease accompanied by renal and cerebral impairment.

Other factors which need to be addressed are oxidative stress, excess salt intake, clotting disorders, smoking, and hyperhomocysteinemia. These are measures that encompass many organs, mainly the kidney, heart and brain.

Uremia is a microinflammatory state and requires renal replacement therapy, thereby improving renal and cardiac injury, as well as that of other tissues and organs. Because these factors are beyond single organ protection they belong to multiorgan protection.

Therefore, overlapping pathology which afflicts many systems can be reframed as multiorgan protection, allowing for a unitary approach. (Fig. 1) Cytoprotection and molecular protective measures could be added.

## **CHRONIC KIDNEY DISEASE AND CARDIOPROTECTION**

Chronic kidney disease is accompanied by cardiovascular involvement; contributing factors to this condition are elevated blood pressure, metabolic disturbances with subsequent coronary atherosclerosis, endothelial damage, hypoxia secondary to anemia, oxidative stress, etc.

It is assumed that for a patient with chronic kidney disease the probability to reach end-stage renal disease (ESRD) should be lower than the probability to die from cardiovascular complications (K/DOQI 2002).<sup>3</sup> Atherosclerosis starts during the first stages of chronic kidney disease and worsens during hemodialysis. Locatelli et al. have shown that cardiovascular diseases play a major role in the morbidity and the mortality of patients undergoing renal replacement therapy, representing 50% of all cause mortality rate.<sup>4</sup> Rabelink et al. consider cardiovascular death in patients with ESRD to be probably the highest encountered in medicine.<sup>5</sup> CKD is considered an independent risk factor for cardiovascular diseases.<sup>6</sup> Mortality rate related with cardiovascular diseases increases with declining glomerular filtration rate (GFR).<sup>7-9</sup>

CKD defined as reduced GFR below 60 ml/min/sqm has been designated as a major risk factor for cardiovascular disease in JNC VII and the European Society of Hypertension.<sup>10</sup> CKD represents also an independent factor for the progression of atherosclerosis. Atherosclerotic lesions in the thoracic aorta have been significantly higher in uraemic E-/-

mice than in non-uremic controls. CKD increases arterial calcifications at sites of the internal wall of vessels affected by atherosclerosis as well as at atheroma-free sites.

CKD seems to have systemic consequences; therefore it can be considered a systemic disorder. It is estimated that out of 8 million Americans affected by CKD who have not undergone renal replacement therapy, 80% will die of cardiovascular causes. The probability of cardiovascular death is higher than that of reaching ESRD even for patients with mild and moderate renal function impairment.<sup>8,11</sup>

Some of the mechanisms encountered in CKD are known to generate systemic alterations. It is considered that kidney has a central part in controlling blood pressure through regulation of Na absorption and through renin-angiotensin system which metabolises catecholamines. The plasma concentration of renin is reduced in patients with ESRD, inducing an increase in arterial blood pressure and changes of cardiac function.<sup>12</sup>

Patients with cardiovascular diseases frequently show renal injury, which has not yet been studied in its complexity. Nephroangiosclerosis is a common occurrence during arterial hypertension. Renal involvement has also been signaled in many cardiovascular diseases, although there is a relative paucity of data regarding the impact of kidney lesions in cardiovascular diseases.

In a study performed by Adler et al. who have followed up 5097 patients over a period of longer than 10 years, with type 2 diabetes, it has been proven that the risk of death through cardiovascular disease is greater than that of developing ESRD.<sup>11</sup>

Lately, the term of cardio-renal failure has gained momentum. This draws attention to the simultaneous and often severe affection of both cardiac and renal function.<sup>13</sup>

Cardioprotective measures represent cardinal elements during the treatment of CKD. Because the majority of renal diseases show an involvement of the cardiovascular system, mainly during ESRD, they are as mandatory as nephroprotective measures. By targeting both systems they sometimes overlap.

## **THE KIDNEY AND THE VASCULAR ENDOTHELIUM**

The kidney is an organ which can target the vascular endothelium in different ways:

- Hypertension of renal origin through elevated blood pressure, Angiotensin II, endothelin and vasopressin.

- Microinflammatory processes:

- CKD represents a chronic inflammatory state per se.

- End stage renal disease generates also chronic inflammation which affects the vascular bed. It is regarded by Luke et al. as a chronic vasculopathic state; with malnutrition as a major contributor.<sup>14</sup>

- Atheromatosis, a common occurrence in CKD, mainly in the advanced stages, is presently considered a microinflammatory process.

- Nephrotic syndrome is accompanied by disturbances of lipid metabolism which affect the vascular endothelium.

CKDs, most commonly the nephrotic syndrome, are accompanied by clotting disorders, which lead to an increase in the procoagulant activity. Renal diseases also show disturbances in the synthesis of NO at the level of arterial blood vessels, of cGMP and of glycosaminoglycans. Asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide, accumulates during CKD following functional decline. ADMA accelerates endothelial senescence by inhibiting telomerase activity, thus favoring atherosclerosis.<sup>15</sup>

According to Schiffrin, microalbuminuria can evolve in hypertensive patients parallel to endothelial damage and AHT progression.<sup>16</sup>

In renal disease drugs with endothelial protective properties are employed, such as sulodexide. These drugs have nephroprotective effect by reestablishing the balance of renal glycosaminoglycans. At the same time they reduce proteinuria exhibiting a nephroprotective effect. As they target vascular endothelium in general they exert multiorgan protective actions.

## **PROTEINURIA AND NEPHROPATHY**

Proteinuria is strongly related to kidney disease progression. It is involved in tubulo- interstitial lesions from glomerular diseases.

Inflammatory glomerular diseases are accompanied by the excretion of serum proteins. These can cause tubulo-interstitial damage by different pathways:

- Protein overload induces NF-KB activation in proximal tubular cells.

- Elimination of cytokines and chemokines produced in the course of the inflammatory process at the level of the glomerulus and other mediators of the inflammation.

- Elimination in the urine of components of the complement system.

- Synthesis and release of chemokines by tubular

cells, which will attract macrophages.

- Filtered proteins in the glomerulus lead to proliferation of the proximal tubular cells, which will cause attraction of macrophages

- Filtered proteins in the glomerulus lead to the proliferation of proximal tubular cells associated with the increase of the synthesis of vasoactive and proinflammatory substances.

At the same time, proteinuria has more general effects on the circulatory system with an impact on brain, heart and kidney. Heavy proteinuria during the course of nephrotic syndrome can cause important tubulo-interstitial inflammatory lesions. They will also concomitantly affect the lipid profile leading to increased levels of triglycerides and VLDL cholesterol, and reduced serum lipoproteinlipase activity. Proper conditions for the development of atherosclerosis within the vascular walls will be created. Consequently, patients with nephrotic syndrome will show more often atherosclerotic changes at the level of the coronary arteries, as well as cerebral and renal arteries. Moreover, patients with advanced CKD show lipid profile disturbances, which progress with the evolution of the disease, with the predominance of hypertriglyceridaemia, which could explain atherosclerosis in these patients.

Even mild proteinuria or microalbuminuria could play a role in the pathological processes taking place at the level of the vascular tree. In diabetes mellitus it correlates with the endothelial lesions.

## **ANEMIA OF RENAL ORIGIN AND NEPHROPROTECTION**

Reduction of the renal parenchyma creates a relative deficiency of erythropoietin with subsequent anemia. The severity of anemia grossly approximates the severity of renal dysfunction and reduction of nephron mass.

Anemia is a common element of advanced CKD but also accompanies mild impairment of renal function.

It is considered that a patient with mild or moderate CKD has a higher propensity to die of cardiovascular cause than of reaching ESRD. Conversely, a patient with heart disease frequently develops kidney involvement which can aggravate cardiac disease. If associated to both conditions, anemia is a worsening factor.

Strippoli et al., by analyzing many clinical trials of patients with variable degree of cardio-vascular involvement, observed a higher mortality rate in those with concomitant renal and heart disease, related to hemoglobin levels.<sup>17</sup>

Anemia is associated to left ventricle hypertrophy, increased vascular morbidity, progressive decline of renal function, decrease of cognitive ability, etc.

Anemia acts as a multiplier of overall mortality at any hemoglobin decline below 12 g/dl. Mortality increases in patients with CKD and heart disease. Cardiovascular risk factors play a key role in the development of CKD and vice-versa.<sup>18</sup> The metabolic syndrome can lead to cardiovascular disease and kidney impairment without overt diabetes.

The addition of anemia to CKD is associated with an increased risk for stroke independently of other risk factors. This has been shown in ARIC (Atherosclerosis risk in communities) on 13716 investigated persons.<sup>19</sup> An increase in hemoglobin to levels above 10 g/dl is related to an improvement of cardiac performance and the regression of heart enlargement.<sup>20,21</sup>

### **CONCOMITANT RENAL, CARDIAC AND CEREBRAL INJURY**

Renal, cardiac and cerebral organ lesions and the therapeutic measures with for them have been the object of numerous studies, some of them multicentric clinical trials. These studies are aimed either towards a single organ (heart, kidney, brain) or an association of two organs (kidney and heart, heart and brain) or investigated an association of the three organs: kidney, heart and brain, as well as other associations. A small number of studies are addressed to the association of the three organs: brain, heart, kidney.

The HOPE study (Heart Outcome Prevention Evaluation Study) has demonstrated the effect of ramipril (angiotensin converting enzyme inhibitor) compared to placebo in patients at high risk of cardiovascular events. Ramipril reduced the rates of myocardial infarction, stroke and cardiovascular death.<sup>22</sup>

The concomitant injury of more than one organ related to renal disorders has been demonstrated in two of our studies. The first was performed on a group of 547 patients with chronic renal failure in the predialytic phase, admitted to the Department of Nephrology, Timisoara, between 1991 and 2002; 191 of them were followed up during a mean period of  $19.38 \pm 23.55$  months, concerning the relationship with hypertension. We observed that 458 patients (83.72%) had hypertension, 288 of them had hypertensive cardiopathy (56.65%) and 8 cases had a history of stroke.

Hypertension is a proven risk factor. Patients with CRF and hypertension have a degradation

rate of renal function (delta creatinine clearance) higher than patients without hypertension:  $21.97 \pm 18.68$  ml/min as compared to  $15.6 \pm 10.5$  ml/min ( $p < 0.05$ ). The association of risk factors (proteinuria, hypercholesterolemia) for CRF progression generated degradation of the renal function significantly higher than the isolated risk factors.<sup>23</sup> Our study has underlined the fact that, in order to prevent renal, cardiac and cerebral lesions, some measures of nephroprotection, cardioprotection and neuroprotection are necessary. The common protection of the three organs is defined as multi-organ protection. These measures could influence proteinuria.

In a prospective study, we followed up the reno, cardio and cerebrovascular protective effects of perindopril in patients with primary chronic glomerulonephritis. A 12 month-study with ACE inhibitor perindopril was conducted on a group of 21 patients with primary chronic glomerulonephritis with normal renal function or mild renal impairment admitted to the Department of Nephrology, in Timisoara. Cardiovascular and cerebrovascular effects of perindopril were monitored by ultrasound (left ventricular hypertrophy, left ventricular mass, E/A ratio, ejection fraction, isovolumic relaxation time), extracranial Doppler ultrasonography (pulsatility index- internal carotid artery), transcranial Doppler (PI – middle cerebral artery).

The effect on renal function was monitored through the following parameters: creatinine clearance, serum creatinine, serum Na, serum K, proteinuria.

Perindopril proved to be effective in lowering blood pressure, correcting left ventricular hypertrophy and mass. The ejection fraction showed little change. The cerebroprotective effect was proven by the decrease of the pulsatility index (a measure of vascular distensibility and compliance through the ratio systolic velocity- diastolic velocity/ mean velocity). Although proteinuria declined from  $5.57 \pm 1.0$  g/24 h to  $1.02 \pm 0.36$  g/24, the nephroprotective effect of this drug is less in terms of creatinine clearance, the latter decreasing after 12 months from  $81.85 \pm 11.27$  ml/min to  $76.42 \pm 9.56$  ml/min.<sup>24</sup>

### **NEPHROPROTECTIVE MEASURES WITH MULTIORGAN EFFECTS**

Because the kidney, heart and brain are affected by common risk factors, protective measures are not possible by monotherapy. Two approaches are used: organ and multiorgan protection. The use of drugs which address multiple risk factors is advisable.

ACE inhibitors and AII receptor blockers have a hypotensive effect with subsequent renal, cardiac and cerebroprotective actions. At the same time they exert an antiproteinuric effect, mainly on renal blood flow. Concomitantly, statins have a lipid-lowering effect which acts protectively on the coronary cerebral and renal blood supply.

Another approach is the association of multiple drugs targeting different risk factors, resulting in multiorgan protection. Thereby, complex protection can be achieved, because many risk factors are shared by the kidney, heart and brain. The most commonly prescribed associations are:

- Single pill: aspirin, statin, 3 blood pressure lowering drugs at half dosage, and folic acid as proposed by Law et al.<sup>25</sup>

- A super-pill: ACE inhibitors, ARBs, diuretics, non-dihydropyridine calcium channel blockers.<sup>26</sup>

- A combination of aspirin, lovastatin, lisinopril which has been named ASTACE (aspirin, statin, ACE inhibitor).<sup>27</sup>

We will briefly summarize some of the drugs with nephroprotective effect which possess cardiac, neurological and also multiorgan protective actions. These drugs also exert cytoprotective and molecular protective effects.

### **ACE inhibitors and Angiotensin II receptor blockers (ARB)**

They exert actions on the vascular tree at the level of different organs ensuring renal, cardiac and cerebral protection. Blood pressure lowering is their main action. These drugs have a cardioprotective effect by improving cardiac function after myocardial infarction, reducing cardiovascular morbidity and mortality as shown in HOPE study.<sup>22</sup> A better effect on morbidity and mortality has been reported with ARBs compared to other hypotensive drugs at the same level of blood pressure reduction.<sup>28</sup>

ACE inhibitors and ARBs also demonstrated neuroprotective action - prevention of stroke, and nephroprotective effects - they slow the progression of renal disease.<sup>6</sup>

The antiproteinuric effect is produced by lowering intraglomerular pressure and modification of glomerular capillary permeability and increases upon association to ARBs of ACE inhibitors.<sup>29,30</sup> They have a nephroprotective effect in both hypertensive and normotensive individuals, which could be partly explained by the reduction of proteinuria.<sup>31</sup> ARBs have a positive effect on renal fibrosis by collagen synthesis blockade.<sup>32</sup>

### **Treatment with statins**

Their main action consists of blockade of cholesterol synthesis, thereby exerting strong lipid-lowering effect. Besides, statins have pleiotropic effects, such as the following: reduction of NFκB activation, anti-inflammatory action, anti-oxidant effect, hypotensive effect, by down regulation of AII receptor type I, improvement of endothelial function by means of up-regulating endothelial cell NO synthase, reduction of reactive oxygen species in the vascular wall, and antiproteinuric effect: cerivastatin has been reported to reduce microalbuminuria in patients with type II diabetes mellitus.<sup>33</sup> The blood pressure lowering effect can contribute to the reduction of albuminuria. The combination of statins with ACE inhibitors diminishes glomerulosclerosis and protein excretion in the Heymann nephritis model in rats, while ACE-inhibitors or statin monotherapy has limited effects.<sup>34</sup>

HMG-CoA reductase inhibitors improve diabetic nephropathy through pleiotropic effects in rats.<sup>35</sup> Lovastatin inhibits mesangial cell proliferation in rats, while cerivastatin prevents ICAM 1 expression.<sup>36</sup> Statins selectively block LFA-1 mediated adhesion and costimulation of lymphocytes.

### **Erythropoietin (EPO)**

It is a cytokine mainly produced by the kidney with stimulating effects on erythropoiesis. Furthermore, erythropoietin demonstrated tissue-protective effects in an experimental model of ischemic-induced neuronal, retinal, cardiac and renal lesions.<sup>37</sup> With the exception of its stimulating effect on erythropoiesis, the other effects occur at increased concentrations which are different from those therapeutically employed for the correction of anemia.

The nephroprotective effect of EPO has been demonstrated in the ischemia/reperfusion model in rats and mice and is related to apoptosis.

The cardioprotective effect is produced by EPO receptors. EPO prevents myocyte apoptosis; apart from the effect on cardiac myocytes, it acts on endothelial progenitors and on hematopoietic stem cells.<sup>18</sup> EPO has cardioprotective actions in ischemia/reperfusion injury in rats.<sup>38</sup> It reduces myocardial infarction after ligation of coronary arteries in rats. Experimental data in dogs have shown EPO to reduce lethal arrhythmia and size of infarction.<sup>39</sup> EPO induces myocardial neovascularization. Through correction of anemia it leads to regression of left ventricular hypertrophy in patients with predialytic advanced CKD, as well as in dialysed hypertensive

and normotensive individuals.

EPO has a neuroprotective action by exerting an important cytoprotective effect at the level of the nervous system. Of note, EPO is expressed at neuronal level. Astrocytes have been shown to produce EPO. Neurotrophic effect is related to the inhibition of apoptosis. EPO has a proven effect in acute stroke.<sup>40</sup> It promotes neuronal survival favoring the transcription of brain derived neurotrophic factor (BDNF).<sup>41</sup>

EPO possesses a myriad of effects on immune reactions: inhibition of inflammatory cytokine release and of inflammatory cell infiltration.<sup>42</sup>

### Sulodexide

It represents a mixture of glycosaminoglycans (GAGs) composed of heparan sulphate 80% and dermatan sulphate 20%. It can stabilize endothelial cells and has antiproliferative effects on smooth muscle cells. Moreover it has antithrombotic properties and promotes fibrinolysis, and also diminishes oxidative stress in diabetic patients.

It possesses cardio-, neuro- and nephroprotective effects. The cardioprotective effects are manifest on ischemic myocardium by protecting the ischemic heart from ischemia/ reperfusion injury.<sup>43</sup> Neuroprotective action is represented by the inhibition of neointimal proliferation of the carotid artery in rats.

GAGs are essential for the maintenance of glomerular charge selectivity. The administration of GAGs results in reduced albuminuria in diabetic patients.<sup>44</sup> Sulodexide therapy reduces proteinuria in different types of glomerulonephritis other than diabetic nephropathy.<sup>45</sup> In glomerulopathies, an abnormal GAG metabolism is involved at the onset of morphological and functional alterations.

In conclusion, organ-protective measures included in nephro-, cardio- and neuroprotection, as well as measures of cyto- and molecular protection overlap. They keep the specificity of the organ, but at the same time, most of them outstretch the domain of regional pathology, defining multiorgan protection.

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