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PROGRESSION PREVENTION STRATEGIES IN CHRONIC RENAL FAILURE AND HYPERTENSION

AN EXPERIMENTAL AND CLINICAL STUDY

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II Y. Pechter, J. Maaroos, M. Zilmer, K. Zilmer, S. Mesikepp, A. Veraksits, M. Ots „The Impact of Aquatic Exercise on Cardio-respiratory, Renal and Lipid Parameters in Chronic Renal Failure Patients" Monduzzi Editore International Proceedings Division ATHEROSCLEROSIS: Risk factors, Diagnosis and Treatment, Salzburg, July 7–10, 2002: 67–70

III Ülle Pechter, Jaak Maaroos, Siiri Mesikepp, Alar Veraksits, Mai Ots "Regular Low-intensity Aquatic Exercise Improves Cardiorespiratory Functional Capacity and Reduces Proteinuria in Chronic Renal Failure Patients" Nephrology Dialysis. Transplantation, 2003, 18,3:624–625

IV Ülle Pechter, Mai Ots, Siiri Mesikepp, Kersti Zilmer, Tiiu Kullissaar, Tiiu Vihalemm, Mihkel Zilmer and Jaak Maaroos "Beneficial Effects of Water-based Exercise in the Patients with Chronic Kidney Disease" International Journal of Rehabilitation Research, 2003, 26(2):153–156

ABBREVIATIONS

AH	arterial hypertension
AngII	angiotensin II
AT	atenolol
BP	blood pressure
CRF	chronic renal failure
CVD	cardio-vascular diseases
EH	essential hypertension
ESRD	end-stage renal disease
FSGS	focal-segmental glomerulosclerosis
GFR	glomerular filtration rate
GSH	reduced glutathione
GSSG	oxidized glutathione
GSSG/GSH	glutathione redox ratio
HDL	high-density lipoprotein
IF	interstitial fibrosis
OxS	oxidative stress
LPO	lipid peroxidation
VLDL	very low-density lipoprotein
LDL	low-density lipoprotein
LOS	losartan
MDA	malondialdehyde
RAS	renin angiotensin system
RF	renal failure
TGSH	total glutathione
VO_2max	peak oxygen uptake
5/6NPX	sub-total (5/6) nephrectomy

1. INTRODUCTION

Chronic renal failure (CRF) represents a progressive, irreversible decline in the glomerular filtration rate. Progressive renal function loss is a common phenomenon in renal failure, irrespective of the underlying cause of the kidney disease. Most chronic nephropathies lack a specific treatment and progress relentlessly to end-stage renal disease (ESRD) which prevalence thereof is increasing worldwide (Locatelli *et al.* 2001; Moeller *et al.* 2002).

CRF patients are almost invariably hypertensive (Ridao *et al.* 2001), have acquired combined hyperlipidemia and hyperhomocysteinemia (Beto and Bansal 1998), profound oxidative stress (OxS) (Annuk *et al.* 2001), and decreased physical activity and increased psychosocial problems. If patients choose to smoke, the additive risk is profound (Orth and Ritz 2002). Diabetes mellitus is a major risk factor for both cardiovascular diseases (CVD) and CRF (Ritz *et al.* 1999). Moreover, CRF patients are becoming older and are often menopausal (Wenger 1998; Jang *et al.* 2001; Shlipak *et al.* 2001). Finally, renal patients have a dramatic tendency for vascular and cardiac calcification, probably related mainly to hyperparathyroidism (Llach and Velasquez Forero 2001; Drueke and Rostand 2002; Fatica and Dennis 2002; Amann *et al.* 2003). Also, the risk of atherosclerotic CVD in patients with CRF, especially in patients on renal replacement therapy, has shown to be 10–20 times greater than in the general population (Foley *et al.* 1998; Levey *et al.* 1998; Luft 2000; Eknoyan *et al.* 2001; Sarnak *et al.* 2002).

Experimental studies have shown that lipid abnormalities can influence the progression of renal disease and lipid peroxidation (LPO) has been increased in animal and human glomerular diseases (Nath *et al.* 1990; Schrier *et al.* 1994; Annuk *et al.* 2001). Reactive oxygen species (ROS) increased production in nephron leads to renal tissue elevated LPO. Profound LPO in vessels and later development of atherosclerotic lesions play a central role in the progression of the pathology (Ross 1999). Uraemia is associated with the generation of profound OxS, which has impact on highly rapid development of atherosclerosis and is related with consequences in target organs (Galle 2001; Himmelfarb *et al.* 2002).

Reduction of both the traditional atherosclerosis risk factors as well as specific factors related to chronic renal failure should be one of the main targets of early management of patients with chronic renal disease (Sarnak and Levey 2000; Taal and Brenner 2001; Ritz *et al.* 2002). The National Kidney Foundation Task Force recommendations stress the importance of preventive measures for renal patients, early in the course of kidney failure, when these can be most effective, cost efficient, and of greatest benefit to patients and to society (Ismail *et al.* 1998; Meyer and Levey 1998). The notion of renoprotection is developing into a combined approach to renal diseases; the main goals are control of blood pressure and reduction of proteinuria (Grimm *et al.* 1997; Ruggenenti *et al.* 2001; Praga and Morales 2002).

Renin-angiotensin system (RAS) blocking agents have been proved to be vaso- and renoprotective and, therefore, suggested not only for anti-hypertensive but also for vaso- and cardio-protective purposes in chronic glomerular diseases with and without systemic hypertension (Ruilope 1997; Cruickshank 2002; Fournier *et al.* 2002; Pisoni *et al.* 2002). Angiotensin II is a potent stimulator of OxS and renin-angiotensin system blocking agents may reduce the profound OxS in the body (Donmez *et al.* 2002; Agarwal 2003). How different RAS blocking agents implicate OxS levels in blood, urine and kidney tissue needs still further investigation.

As patients with chronic renal disease are considered in the highest risk group of premature atherosclerotic cardiovascular events, all beneficial cardiovascular rehabilitation strategies should be included in their management, in addition to pharmacological renoprotective therapies (Ots *et al.* 2000) in order to retard the development of risk factors for CVD and stabilise renal functioning for a longer period of time (Oberley *et al.* 2000). Preventive measures should be undertaken as early as possible. The care of CRF patients cannot start in the period of ESRD or after the initiation of dialysis, but should be set in motion when progressive renal disease is diagnosed and renal failure first begins.

Therapy that diminishes the activity of the renin-angiotensin system and the sympathetic nervous system could possibly stabilise kidney functioning (Ritz *et al.* 1998; Amann *et al.* 2001; Orth *et al.* 2001; Augustyniak *et al.* 2002).

Aerobic exercise, of moderate intensity, is associated with beneficial hemodynamic response and reduction of sympathetic activity (Brown *et al.* 2002; Gajek and Zysko 2002; Svarstad *et al.* 2002). Some experimental studies have shown that exercise in a water environment could improve renal functioning and even slow the progression rate (Heifets *et al.* 1987; Osato *et al.* 1990). Land-based exercise studies have not yet shown a benefit on renal function neither in clinical (Eidemak *et al.* 1997) nor in experimental studies (Averbukh *et al.* 1992; Bergamaschi *et al.* 1997). Exercise therapy for renal patients is usually taken with precaution because of exaggerated renal vasoconstriction during exercise (Clorius *et al.* 2002).

There is still much effort needed to study the mechanisms involved in the progression of kidney diseases to find out the best possible progression prevention strategies of combinations of drug interventions and lifestyle changes.

The present work consists of studies that evaluate the modulation of OxS parameters in experimental and clinical progressive renal failure with pharmacological and non-pharmacological ways of treatment. The experimental part of this thesis investigates the OxS indices in small animals to estimate the changes in OxS grade in blood, urine and kidney tissue using RAS-blocking therapy with losartan and RAS independent beta-blocking therapy with atenolol. The clinical part of the study evaluates the impact of rehabilitation conditioning program on OxS in CRF patients and elucidates the benefits of the conditioning on renal and cardio-respiratory parameters.

2. REVIEW OF THE LITERATURE

2.1. General characteristics of progressive renal disease

Virtually, renal diseases progress to terminal renal failure (RF) relatively independently of the initial disease. The most common causes of progressive CRF are diabetic nephropathy, chronic glomerular diseases and hypertensive nephrosclerosis (Remuzzi *et al.* 1997). A primary disease eventually leads to secondary glomerular injury and nephron loss that is clinically characterised by proteinuria, hypertension, a gradual elevation in the plasma creatinine concentration and a progressive decline in glomerular filtration rate (GFR) (Jacobson 1991). Various risk factors and mechanisms contribute to the pathogenesis of RF where participation of the RAS (Wolf *et al.* 2003), sympathetic overactivity (Johansson *et al.* 1999; Amann, Koch et al. 2001) and developing of proteinuria play central roles (Schmitz and Vaeth 1988; Keane 2000) (Fig.1).

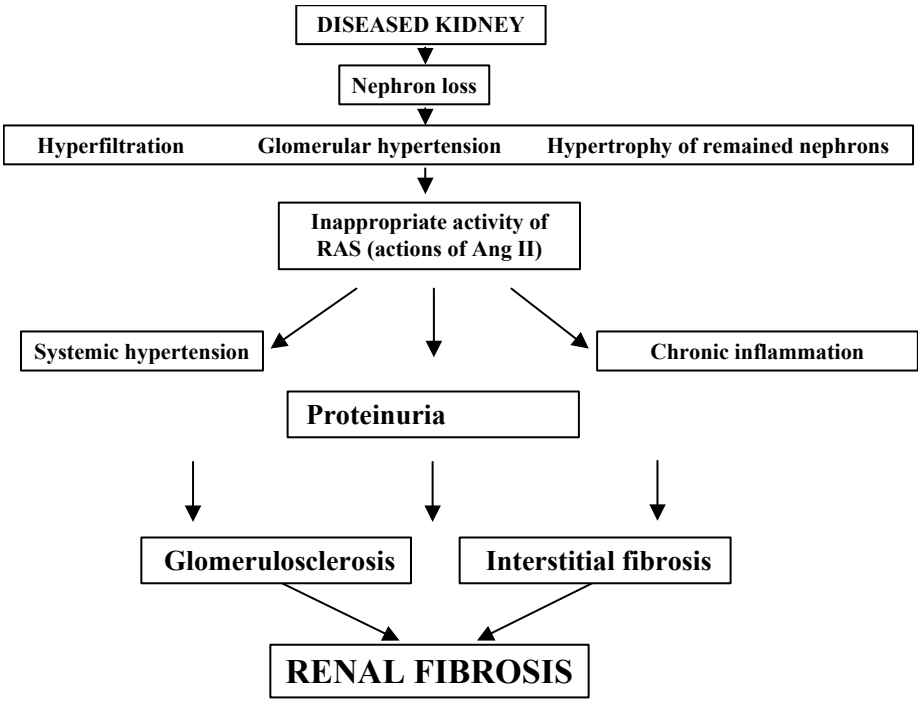

Figure 1. Pathogenesis of renal failure. RAS — renin-angiotensin system; AngII — angiotensin II

In the great majority of cases, progression to ESRD occurs slowly over a period of several to many years. Proteinuria is the earliest clinical marker of hemodynamically mediated glomerular injury (Peterson *et al.* 1995). The findings that greater proteinuria and significant hypertension are independent predictors of accelerated progression of renal dysfunction are confirmed previously (Hunsicker *et al.* 1997; Ruggenenti *et al.* 1998).

Although the underlying renal disease often cannot be treated, the progression of chronic renal disease greatly depends on systemic and intra-glomerular hypertension, dyslipidemia, OxS and development of glomerular damage and therapeutic interventions suppressing these factors may be successful in slowing the progression rate of CRF, regardless of the initiating cause.

2.2. Risk factors of premature atherosclerotic complications in chronic renal disease

In addition to classical risk factors of premature atherosclerotic complications for all population (aging, male gender, hypertension, diabetes, dyslipidemia, smoking, physical inactivity) patients with CRF have specific risk factors: inappropriate activity of Ang II, uremic toxicity (including hyperuricemia and hyperphosphatemia), prolonged high-grade OxS, malnutrition, anemia and immunosupressive treatment (Stenvinkel *et al.* 1999). Psychosocial factors, such as environmental stress and lowered responsiveness to stress should not go unmentioned (Suh *et al.* 2002).

The progression of atherosclerosis is prescribed previously (Ross 1999; Lusis 2000). The approach to the risk factors like hypertension, diabetes, obesity, hyperlipidemia, profound OxS, smoking and physical inactivity should be guided by the principle that chronic renal disease patients belong in the highest risk group for subsequent atherosclerotic complications (Baigent *et al.* 2000; Zoccali *et al.* 2002).

2.2.1. The renin-angiotensin system and pathogenic roles of angiotensin II

Angiotensin II (Ang II), the principal peptide of the RAS, is an important factor in mediating glomerular haemodynamics and contributes to the rise of intraglomerular and systemic blood pressure. Although there are numerous mechanisms involved in the process of renal disease progression, however, the RAS plays a crucial role there (Aros and Remuzzi 2002; Wolf, Butzmann et al. 2003).

Activation of RAS increases the levels of Ang II in the plasma, leading to generalised vasoconstriction and to salt and water retention in the kidneys. Simplified RAS is an enzymatic cascade (Fig 2) in which renin acts on angiotensin to form Ang I and the latter is converted to Ang II by the angiotensin converting enzyme (ACE). Ang II interacts with at least two membrane receptors, type 1 (AT_1) and type 2 (AT_2).

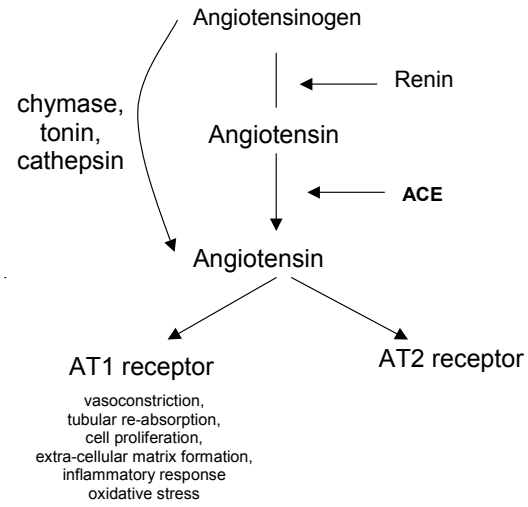

Figure 2. Renin-angiotensin system (RAS).

The AT_1 receptor is responsible for the majority of the effects of Ang II: vasoconstriction, sodium re-absorption, modulation of OxS, cell proliferation and inflammatory response (Luft 2002; Sun *et al.* 2002). The AT_2 receptor has a similar structure, but its transduction and function is less known. Probably a certain amount of Ang II can be produced via non-ACE pathways (by chymase, tonin, cathepsin). Therefore, the modulation of level of Ang II is physiologically important and AT_1 receptors are responsible for angiotensin's functional effects (Luft 2002).

Ang II is both an endocrine hormone in blood and a paracrine hormone formed in tissue. The paracrine way of RAS is noticed in almost every tissue, especially in brain, cardiac and renal tissue. Most renal AT_1 receptors are exposed to locally produced Ang II rather than to Ang II from circulation. However, both local production and AT_1 receptor-mediated uptake from the circulation contribute to the high levels of Ang II in the kidney (Kim and Iwao 2000; van Kats *et al.* 2001; van Kats *et al.* 2001).

Ang II may promote renal disease progression by inducing glomerular hypertension, hyperfiltration, glomerular hypertrophy (Brenner 1983) and leading to increased systemic blood pressure (Aros and Remuzzi 2002). On the

other hand, Ang II behaves like a proinflammatory cytokine, participating in various steps of the inflammatory response: induces expression of monocyte chemo-attractant protein-1, a potent chemokine (Wolf 1998; Kato *et al.* 1999), osteopontin expression (Yu *et al.* 2000), proliferation of mesangial and glomerular endothelial cells (Yu 2003) and over-production of transforming growth factor-beta (Shin *et al.* 2000) contributing to pathological inflammation and fibrosis through the accumulation of extracellular matrix proteins (Sun *et al.* 2000; Mezzano *et al.* 2001). Ang II increases plasminogen activator inhibitor-1 (Paueksakon *et al.* 2002) favouring thrombosis and progressive sclerosis (Ma and Fogo 2001). Haugen *et al.* (2000) and Pueyo *et al*. (2000) have shown that Ang II is contributing to pathologically increased OxS level, activating inflammatory mechanisms (Haugen *et al.* 2000; Pueyo *et al.* 2000). So, Ang II exerts both hemodynamic and non-hemodynamic effects on the kidney, which are involved in the loss of renal function.

2.2.2. Hypertension

Kidney disease may be either a cause or consequence of hypertension and atherosclerotic CVD (Prichard 2003). Hypertension is a significant risk factor for the development of glomerulosclerosis in various etiologies (Klag *et al.* 1996; Ridao, Luno et al. 2001). According to the data of three large registries covering the United States, Europe, and Australia / New Zealand it appears that hypertension and diseases of the large arteries constitute the second major cause of RF (Maisonneuve *et al.* 2000). In Estonia, the prevalence of ESRD caused by hypertension is low, 7% (Lilienthal *et al.* 2003).

Essential hypertension (EH) is a multi-factorial disorder that involve abnormalities in the functions of the heart, the blood vessels, the kidneys and is characterised by significant and persistent elevations in arterial BP (Bakris and Mensah 2002). Primary or EH is diagnosed by exclusion, as the cause of hypertension is not readily definable. Approximately 5–10% of patients have secondary forms of hypertension. Renal parenchymal disease is the most common pathology associated with hypertension. Renovascular hypertension due to renal artery stenosis is the most common potentially curable form of hypertension with the help of angioplasty, stenting or surgery. Pathology in endocrine organs causes endocrine hypertension. The use of medications, oral contraceptives, an excess of alcohol and drug abuse cause reversible rises in blood pressure (BP).

Essential hypertension

In the development and maintenance of EH the genes, environment and the gene-environment interactions play key roles. High salt intake influences the formation of EH in approximately 1/3 of hypertensive patients, in so called "salt-sensitive" persons. Recently has been shown that high salt diet may via OxS-associated mechanism (including glutathione system) induce endothelial dysfunction in salt-induced experimental hypertension (Bayorh *et al.* 2004).

Apart from a genetic component more women than men and more urbanites than country dwellers are affected by primary hypertension. In addition, chronic psychological stress, job-related or personality-based, can induce hypertension (Kaplan 1998).

Increases in the heart rate and stroke volume lead to increases in the cardiac output and contribute to increases in arterial BP. Volume status and the level of the total peripheral vascular resistance in combination determine the level of BP.

The systemic vascular resistance is influenced by multiple vasoactive mechanisms under the control of local, regional and systemic neural, humoral and renal factors. The tissue arterioles vasoconstrict to decrease the excessive blood flow. The resulting vasoconstriction raises the peripheral vascular resistance, which is cardinal in most consistent findings in hypertension — whether essential or secondary in origin. If the peripheral vascular resistance is not appropriately lowered in the face of hypervolemia, hypertension results**.** The chronic elevations in BP result from combinations of inappropriate levels of cardiac output and total peripheral resistance.

The kidney is prominent in long-term regulation of BP (Rettig 1993; Mailloux and Haley 1998; Ridao, Luno et al. 2001). The individual changes in cardiac, vascular, or renal function seldom occur separately, and, if so, they may lead to mild or moderate increases in arterial pressure. Combined alterations in cardiac, vascular, and renal functions are more common and are often associated with pathologic increases in arterial pressure and established hypertension (Bakris *et al.* 2000).

The pathophysiological alterations of EH include among others dysregulation of arterial compliance and endothelial dysfunction (Taddei *et al.* 2001), metabolic syndrome and insulin resistance, elevated OxS (Suematsu *et al.* 2002), abnormal sympathetic nervous system activation (DiBona 2002), accelerated atherosclerosis, left ventricular hypertrophy, and a propensity for increased vascular thrombogenesis (O'Donnell *et al.* 1997; Odama and Bakris 2000).

Renal parenchymal hypertension

Hypertension complicates the clinical course of patients with CRF and, if inadequately controlled, may hasten the deterioration of renal function (Mailloux 2001). The development of hypertension among chronic renal disease patients involves various subsequent pathogenic factors, like above-mentioned inappropriate activity of the RAS, increased sympathetic activity, and impaired endothelial vasodilatation (Rettig and Uber 1995; Garg and Bakris 2002).

The fall in GFR during renal disease increases the prevalence of salt-sensitive hypertension. The latter has realations to OxS-associated endothelial dysfunctionality (Pepine and Handberg 2001; Bayorh, Ganafa et al. 2004). Renal disease leads to hypertension, which in turn can contribute to the progressive scarring of the kidney thus playing a pathogenic role in progression of renal disease accelerating loss of function of the diseased kidney (Odama and Bakris 2000). Impaired renal sodium excretion, leading to extra-cellular fluid volume expansion, is the most clinically important mechanism leading to hypertension in those patients with kidney disease (Hostetter *et al.* 2001).

After the loss of a critical number of nephrons, the remaining nephrons undergo compensatory functional and structural adaptations. During this process, the surviving nephrons lose the capacity to autoregulate glomerular flows and pressures and become vulnerable to the effects of systemic hypertension, which is readily accompanied by glomerular hypertension, hyperfiltration and hypertrophy (Hostetter *et al.* 1982), so contributing to the progression of RF (Fig. 1).

Renovascular hypertension

Renovascular hypertension is usually caused by atherosclerotic narrowing of the origin of the renal artery and is common among patients with peripheral vascular disease, carotid stenosis or heart failure. Renovascular hypertension must be distinguished from renal artery stenosis. In true renovascular hypertension, the kidney takes charge of BP and will do what it takes to push blood pressure high enough to force blood through the blocked artery. This can be diagnosed with functional tests that measure glomerular filtration rate before and after blockade of the RAS system with ACE inhibitors or antagonists of the AT 1-subtype of the angiotensin receptor (AT_1RA). Involvment of oxidative stress has been demonstrated in experimental renovascular hypertension (Lerman *et al.* 2001; Higashi *et al.* 2002).

2.2.3. Diabetes

The incidence of diabetes mellitus, particularly type 2, is increasing in the general population. Similarly, the incidence of patients with diabetes mellitus who develop ESRD has increased concomitantly in the dialysis facility to 44% of patients starting dialysis therapy with diabetes mellitus as their primary diagnosis (Ritz and Tarng 2001). According to the data of three large registries covering the United States, Europe, and Australia / New Zealand it appears that diabetic nephropathy is the main cause of end-stage renal disease in many countries (Maisonneuve, Agodoa et al. 2000).

In Estonia, the prevalence of diabetic nephropathy shows increasing tendency, remaining in third place after chronic glomerulonephritis and chronic tubulointerstitial nephritis (Locatelli, D'Amico et al. 2001; Lilienthal, Ilmoja et al. 2003).

Elevated blood glucose causes glomerular hyperfiltration, hypertrophy, and hypertension. Hyperglycaemia induces onset of microalbuminuria both in type 1 and type 2-diabetes (Bakris and Sowers 2002). In the general population and among patients with chronic renal disease, CVD is more prevalent among individuals with diabetes than those without diabetes (Lea and Nicholas 2002). Diabetes and hypertension are the key risk factors for atherosclerotic complications in chronic renal patients whereas both have OxS-based component in their progression pathophysiology (Touyz 2000; Marra *et al.* 2002; Seghrouchni *et al.* 2002; Siems *et al.* 2002; Wen *et al.* 2002).

2.2.4. Pronounced oxidative stress

Under normal physiological conditions, the rate and magnitude of reactive species formation is balanced by the rate of their control/elimination. Generation of oxidative compounds is physiologically relevant as an important step in inflammation and tissue repair processes, it represents part of the defence mechanisms against invading micro-organisms and malignant cells, as well as of tissue healing and remodelling. An imbalance between pro-oxidants and antioxidants results in oxidative stress (OxS), which has the pathogenic outcome when the production of potentially harmful products overwhelms antioxidant capacity/defence (Halliwell and Gutteridge 1999). The subsequent disturbance of the pro- and anti-oxidant balance in favour of the former contributes to tissue injury.

OxS is monitored indirectly by assaying products of oxidative damage (such as lipid peroxidation products, advanced glycation and oxidation lipid and protein products, nucleic acid oxidation derivates) or antibodies directed against oxidized epitopes (such as anti-oxidized low-density lipoprotein antibodies). On the other hand, to investigate the potential of an organism, tissue, cells or body fluids to withstand OxS-caused further events both enzymatic anti-oxidants

(superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic anti-oxidants (glutathione, vitamin C, vitamin E) can be evaluated (Abuja and Albertini 2001).

It has been shown that the overproduction of free radicals and other reactive species plays an important role in the pathophysiology of various experimental and clinical renal diseases (Nath, Croatt et al. 1990; Diamond 1994; Galle 2001; Chade *et al.* 2002; Suematsu, Suzuki et al. 2002; Vaziri *et al.* 2003). The general population studies show that prolonged profound OxS is associated with risk factors for premature atherosclerotic complications, most of them linked to abnormalities in lipid metabolism (Trevisan *et al.* 2001).

Several studies indicate that CRF patients are in a state of pronounced OxS (Kitiyakara *et al.* 2000; Annuk, Zilmer et al. 2001; Boaz *et al.* 2001; Usberti *et al.* 2002). One reason for such OxS in patients with renal failure is the underlying kidney disease itself. Activation of local tissue RAS, renal anaemia and immunological disorders in the kidney result in an elevated formation of reactive oxygen species (ROS) active in the pathogenesis of kidney disease progression. Increased nephron ROS generation leads to renal tissue lipid peroxidation (LPO). An over-activated RAS leads to persistent profound OxS. An interaction between blood pressure, OxS and oxidised lipids (Drueke *et al.* 2001) is proposed as an important key factor that could lead to rapid development of renal and cardiovascular disease (Haugen and Nath 1999; Bolton *et al.* 2001; Annuk *et al.* 2003) (Fig.3).

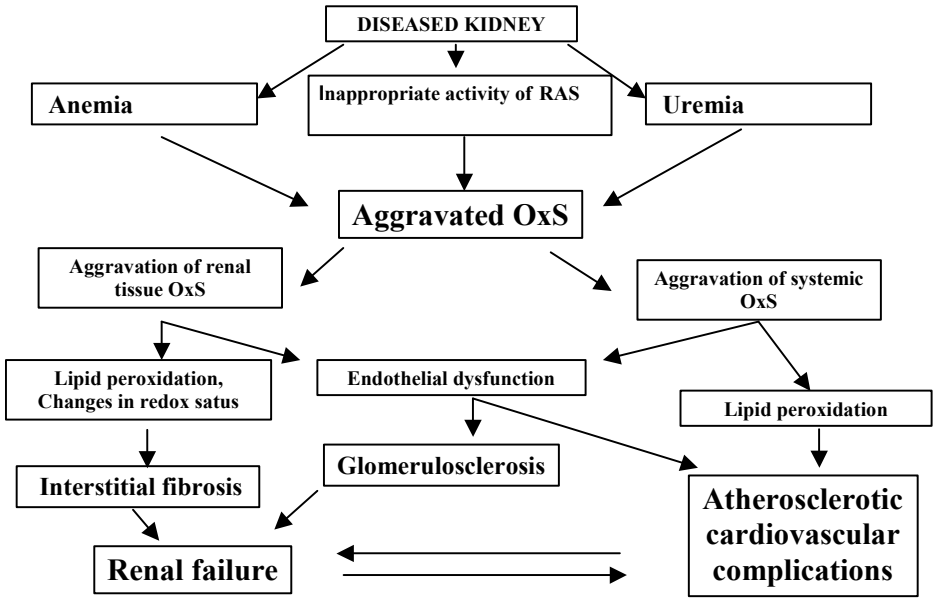

Figure 3. Role of oxidative stress (OxS) in pathogenesis of renal failure

Increased formation of free radicals leads to an accelerated LPO. Both experimental and clinical studies show that the level of LPO is elevated in CRF (Hasselwander and Young 1998; Mathur *et al.* 2002; Selvaraj *et al.* 2002). Secondary aldehydic LPO products (malondialdehyde, MDA and 4-hydroxynonenals) are formed. Isoprostanes are also produced upon peroxidation of lipoproteins (Morrow 2000).

Glutathione (GSH) plays an important role in the cellular defence against oxidant stress (Ceballos-Picot *et al.* 1996; Lang *et al.* 2002). GSH is a major non-enzymatic intracellular antioxidant. Glutathione peroxidaze utilises GSH to reduce lipid hydroperoxides and hydrogen peroxide to their corresponding alchols. Acting as an antioxidant, GSH is oxidised to its disulfide (GSSG). The latter must be rapidly converted back to GSH by glutathione reductase. Hence, the ratio (GSSG/GSH), known as the glutathione redox ratio, may be used to express OxS level in red blood cells and other cells or in blood. In chronic diseases e.g. chronic renal disease, the level of GSH is markedly lowered and the glutathione redox ratio is increased (Lang *et al.* 2000).

Endothelial dysfunction in patients with CRF is a critical component in the systemic vasoconstriction and reduced peripheral perfusion that characterises these patients. Endothelial regulation of vascular tone is mediated substantially by nitric oxide. Increased OxS in CRF is likely caused by decreased bioavailability of nitric oxide due to reduced expression of endothelial nitric oxide synthase and increased generation of ROS (Forgione *et al.* 2002; Vaziri *et al.* 2002).

The decreased vascular relaxation and excessive vasoconstriction lead to significant increases in the peripheral vascular resistance and arterial BP over time, particularly with ageing. The important role of the endothelium and OxS in co-ordinating tissue perfusion has been emphasised by Stenvinkel. Endothelial dysfunction is thus an important target for future therapy in patients with CRF (Stenvinkel 2003).

Because of all above-mentioned reasons, it is plausible that pronounced OxS contributes to the high prevalence of CVD in CRF patients and plays a role in progression of glomerulosclerosis and renal fibrosis. In summary, the common denominators, whereby different risk factors cause atherosclerosis and its consequences in target organs, are elevated OxS, chronic inflammation and endothelial dysfunction.

2.2.5. Sympathetic overactivity

In CRF, sympathetic tone is constantly increased and RAS over-activated. Data from experimental and clinical studies show that sympathetic over-activity is triggered by kidneys and resetting itself by stimulation of hypothalamic centres (Rump *et al.* 1999; Campese *et al.* 2000; Rump *et al.* 2000; Tinucci *et al.* 2001; Ye *et al.* 2002). The damaged kidneys send efferent nerve impulses to the

central nervous system to increase efferent sympathetic discharge (DiBona 2000). Systemically this sympathetic over-activity contributes to hypertension (Campese and Krol 2002) and cardiovascular complications (DiBona 2001; Rabbia *et al.* 2001). Locally in the kidney, neurotransmitter release is enhanced, which induces proliferation thereby promoting loss of renal function. Amann *et al* showed in an experimental study that sympatholytic agent ameliorated greatly hypertensive nephrosclerosis, even in doses, that did not lower BP (Amann *et al.* 2000). In a clinical trial, sympathetic over-activity was normalised during antihypertensive monotherapy with the ACE inhibitor enalapril, but exacerbated by anti-hypertensive therapy with the dihydropyridine calcium channel blocker, amlodipine (Tuncel *et al.* 2002). These results imply a potentially important role for the sympathetic nervous system in explaining recent trial data suggesting an added renoprotective effect of antihypertensive agents that block the RAS. Future clinical trials are needed to determine whether normalisation of sympathetic activity should constitute an important therapeutic goal to improve renal and cardiovascular outcomes in patients with CRF.

2.2.6. Dyslipidemia

Humoral factors, hyperlipidemia, lipid deposition in vessels and later development of atherosclerotic lesions play a central role in the progression of premature atherosclerosis in chronic renal disease (Horsch *et al.* 1981) (Rutkowski *et al.* 2003). In addition to contributing to CVD, pronounced dyslipidemia may be a risk factor for the progression of renal disease. Dyslipidemia and pronounced OxS contribute to premature atherogenesis (Ross 1999). Dyslipidemia of renal disease consists of both quantitative and qualitative abnormalities in serum lipoproteins (Crook *et al.* 2003). Uremic dyslipidemia is mainly characterised by increased plasma triglycerides (Tg), elevated very low-density lipoprotein (VLDL) and decreased high-density lipoprotein (HDL). Plasma total or low-density lipoprotein (LDL) cholesterol is rarely elevated in CRF patients (Shoji *et al.* 2001). The alterations in lipid metabolism and action lead to macrophage activation and infiltration in the kidney with resultant tubulointerstitial and endothelial cell injury. Hyperlipidemia is also an important risk factor for the development of cardiovascular events in CRF patients, and it requires intervention to avoid or minimise the sequeal of these complications (Kasiske 2003). The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are cholesterol-lowering agents that could be well suited to the needs of RF patients (Van Den Akker *et al.* 2003). Studies have shown the effectiveness of statins in lowering LDL cholesterol level, slowing down progression of atherosclerosis (Fried *et al.* 2001), and in decreasing the number of cardiovascular incidents (Tonelli *et al.* 2003). Many circumstances expose the anti-proliferative, anti-inflammatory and even antioxidative

influence of HMG-CoA reductase inhibitors (McKenney 2003). However, in a recent multi-centre trial among renal transplant recipients, therapy with fluvastatin showed no significant impact on risk reduction of cardiac events (Holdaas *et al.* 2003). Since the discovery of statins, experiments and clinical studies have been carried out showing other mechanisms of action by these drugs (Elisaf and Mikhailidis 2002; Yamashita *et al.* 2002; Bianchi *et al.* 2003; Palmer and Alpern 2003) including their nephroprotective role (Tonelli *et al.* 2003; Wilson *et al.* 2003). Future trials will show if there is an effect on cardiovascular mortality and morbidity in CRF patients (Fellstrom *et al.* 2003).
The effects of dyslipidemia on the kidney are mainly observed in those with other risk factors for renal disease progression such as hypertension, diabetes, and proteinuria (Keane 2001; Yu 2003). Nevertheless, high-grade OxS, LPO and elevated LDL oxidation levels are playing here a substantial role (Van Tits *et al.* 2003).

2.2.7. Specific risk factors for uremic patients

The uremic syndrome causes the progressive retention of a large number of compounds, which under normal conditions are excreted by the healthy kidneys (Vanholder *et al.* 2003). They can be conditionally called uremic toxins and they contribute to the progression of atherosclerosis in chronic renal disease. About 90 compounds/factors are described associated with non-physiological influence. High levels of homocysteine (Block *et al.* 1998; Suliman *et al.* 2003), electrolyte imbalance, hyperuricemia and hyperphosphatemia (Locatelli *et al.* 2002) are the most frequently studied. These compounds induce excessive free radical production by renal tubular cells and activate the inflammatory syndrome associated with the development of CRF (Annuk, Zilmer et al. 2003).

2.3. Progression prevention strategies for chronic renal failure

There is a great need to identify complex strategies that arrest the progression mechanisms that contribute to the atherosclerosis development in CRF regardless of the specific renal disease. The most successful advances today are the randomised controlled studies demonstrating the reno- and cardio-protective effects of RAS-blocking therapy (Agodoa *et al.* 2001; Brenner *et al.* 2001; Lewis *et al.* 2001; Wright *et al.* 2002).

Strategies for risk factor identification and reduction should additionally target both the traditional risk factors, including physical inactivity, and specific risk factors related to chronic renal disease. A multiple-risk-factor intervention

is suggested (Levey *et al.* 2003), so that the individual patient could have the proven therapies and best counselling suitable for his personal needs and stage of disease.

2.3.1. Renin-angiotensin system blockade

Studies on experimental (Ots *et al.* 1998) and human diabetic (Brenner, Cooper *et al*. 2001; Lewis 2003) and non-diabetic renal diseases (Maschio *et al.* 1996) revealed that the progression of the renal disease can be slowed by the RAS blockade, which modulates hemodynamic and non-hemodynamic factors contributing to the progression of glomerulosclerosis and renal fibrosis (Ferrario 2002; Strawn and Ferrario 2002).

Therapeutic management of diseases with increased activity of the RAS has been greatly facilitated by the availability of classes of drugs that inhibit ACE or block angiotensin II receptors. In clinical practice, this has had far-reaching implications for the treatment of EH and congestive heart failure (Johnston *et al.* 1979; Turini *et al.* 1979; Palmer *et al.* 2003). Furthermore, RAS-blocking agents have been proved to be vaso- and renoprotective and, therefore, prescribed not only for anti-hypertensive but also for vaso- and renoprotective purposes in diabetic nephropathy and in other chronic glomerular diseases with and without systemic hypertension (Andersen *et al.* 2002). Early intervention in patients with hypertension and diabetes is necessary to prevent the development of kidney damage (Ruilope 2002).

2.3.2. Blood pressure control and the reduction of proteinuria

Systemic hypertension is a strong well-known independent risk factor for impaired renal function (He and Whelton 1999). Lower levels of achieved BP are associated with a slower decline in renal function, both in patients with and without proteinuria (Marcantoni *et al.* 2000; Fournier, Presne *et al.* 2002). The MDRD Study confirmed that a lower blood pressure goal can be regarded as renoprotective: for patients with proteinuria of more than 1.0 g/24 hours, a target blood pressure of less than 92 mm Hg (125/75 mm Hg). For patients with proteinuria of 0.25 to 1.0 g/24 hours, a target mean arterial pressure of less than 98 mm Hg (about 130/80 mm Hg) is advisable (Peterson *et al.* 1995). The extent to which lowering blood pressure reduces proteinuria is a possible measure for the effectiveness of therapy in slowing the progression of renal disease.

Patients with the highest blood pressure and proteinuria are those with the fastest progression of CRF (Grimm *et al.* 1997; Keane 2000). In chronic nephropathies, proteinuria is the best independent predictor of disease progression (Ruggenenti *et al*. 1998; Hebert *et al.* 2001). The level of proteinuria

proved to be the most important risk for progressive kidney injury in diabetic patients (Adler *et al.* 2003; Keane and Lyle 2003). Anti-hypertensive drugs that most effectively limit protein traffic at comparable levels of blood pressure are those that most efficiently slow disease progression and delay or prevent renal failure in proteinuric chronic nephropathies (Usta *et al.* 2003).

Microalbuminuria is one of the earliest indicators of kidney injury (Keane and Eknoyan 1999) and could easily be monitored.

2.3.3. Nutritional counselling

Patients with CRF need to undergo nutritional assessment and their nutritional status should be followed at frequent intervals. A care plan for nutritional management should be developed early in the course of CRF and modified frequently, based on the patient's medical and social conditions (Beto *et al.* 2004).

Lower levels of dietary protein intake slow the increase in proteinuria and renal disease progression both in clinical (Locatelli *et al.* 1991; Maiorca *et al.* 2000; Waugh and Robertson 2000) and experimental studies (Jacob *et al.* 2002; Abbate and Remuzzi 2003). A beneficial effect of low protein diet on the rate of progression of CRF is observed in non-diabetic renal diseases, but their beneficial effect seems to be greater in diabetic renal disease (Aparicio *et al.* 2001).

It has already been emphasized in 1925 by Steiner and Wegman that proteinuria *per se* contributes to the renal tissue injury, and the progression of kidney disease could be influenced by dietary measures that support protein digestion. As reviewed by Schieppati and Remuzzi in 2003, the presence of large quantities of protein within the tubules has an inflammatory effect on the tubular cells and interstitium. Macromolecular trafficking through the glomerulus has an intrinsic toxicity, which is indipendent from the mediation of Ang II as showed in an experimental study with protein overload diet (Benigni *et al.* 2002). Podocytes accumulate protein overload and become damaged, which leads to their dysfunction (Abbate *et al*. 2002). Based on the meta-analyses and secondary analyses of the randomised trials, it can be concluded that protein restriction slows progression of renal disease (Pedrini *et al.* 1996; Zarazaga *et al.* 2001). Patients dietary protein intake could be 0.6 g/kg ideal body weight/day (Locatelli *et al.* 2002). The low protein diet can already be recommended in the early stages of progressive renal disease. Patients on protein-restricted diets should be carefully monitored to prevent malnutrition.

The dietary salt restriction is based on advice given for prevention and treatment of high blood pressure (Ruilope 2004). The goal of 80 to 120 mmol/day (for example, only 2 g sodium/day diet) is considered to be a renoprotective measure. Dietary salt intake could be monitored by a periodic measurement of 24-hour urine creatinine and sodium.

High urine volume and low urine osmolality are independent risk factors for faster GFR decline in patients with chronic renal insufficiency according to the analysis of the MDRD Study database (Hebert *et al.* 2003). The high urine volumes were associated with maintained or increased BP and greater diuretic use. Thus, high fluid intake does not appear to slow renal disease progression. Suggestions are, until better evidence becomes available, that patients with chronic renal insufficiency should generally avoid increased fluid intake.

2.3.4. Control of blood glucose, blood lipids and correction of anemia

The glycemic control in diabetic patients is essential to prevent onset and development of renal involvement (Ritz and Tarng 2001). The renal risk increases progressively with higher HbA1c values.

Hyperlipidemia contributes to the progression of renal disease (Sahadevan and Kasiske 2002). The MDRD Study already showed that low HDL cholesterol was an independent risk factor for progression of renal disease and high cholesterol and high Tg levels promote progression of diabetic glomerulosclerosis (Peterson, Adler *et al.* 1995). 9-year follow-up in Finland (Wirta *et al.* 1997) has shown, that serum Tg predicted total mortality in diabetic patients.

Hyperlipidemia contributes to increased risk of cardiovascular complications. A small but potentially important reduction in cardiovascular risk is achieved with reduction or modification of dietary fat intake, seen particularly in trials of longer duration (Hooper *et al.* 2001). Thus, it is advisable to encourage blood lipid control (Greco and Breyer 1997) and if necessary drug pharmacological treatment in patients with progressive renal disease to correct hyperlipidemia.

Obesity is noticed as a significant risk factor for the development of proteinuria (Tozawa *et al.* 2002). Lowering excess weight is advisable for patients with CRF and motivation to change the dietary habits should result from education.

Kidney tissue hypoxia may be another common mechanism for the progression of chronic kidneys. Progressive anemia, due largely to erythropoetin defiency, is a common complication of CRF (Deicher and Horl 2003). Anemia can be corrected by the administration of erythropoetin and iron preparations. Control and correction of anemia is already essential in pre-dialysis patients, for improving quality of life (Ross *et al.* 2003). On the other hand erythropoetin or iron therapy may transiently enchance the OxS (Locatelli *et al.* 2003). In correction of anemia with erythropoetin or iron therapy, OxS status should be monitored.

2.3.5. Cessation of smoking

Smoking is the number one preventable risk factor of diverse atherosclerotic complications in the world. Several potential mechanisms of smoking-induced renal damage have been discussed, e.g. increase in BP, alteration of intra-renal hemodynamics, as well as activation of the sympathetic nerve, the renin-angiotensin and the endothelin systems (Odoni *et al.* 2002).

The exact mechanisms of smoking-induced renal damage still remain to be determined; the role of profound OxS should be stressed (Lim *et al.* 2001; Wang *et al.* 2002). Discontinuation of smoking has been shown to improve both renal and cardiovascular prognosis in the renal patient and is probably the single most effective measure to retard progression of RF (Schiffl *et al.* 2002). Smoking has vasoconstrictor, thrombotic, and direct toxic effects on the vascular endothelium (Kanauchi 2002).

Cigarette smoking known to be an independent risk factor for progression of inflammatory renal disease (IgA nephritis), non-inflammatory renal disease and diabetic nephropathy (Orth *et al.* 1998; Orth 2002; Chuahirun *et al.* 2003). Smoking is one of the most important remediable renal risk factors. For all the above reasons, cessation of smoking should be advised for renal patients — a recommendation, which should be given more frequently.

2.3.6. Oxidative stress status and adjuvant antioxidant therapy

The development of atherosclerosis in CRF patients seems to be dependant on the grade of oxidative status of lipoproteins and their resistance to oxidation (Mimic-Oka *et al.* 1999; O'Byrne *et al.* 2001). Today, there is no doubt that the control and correction of the oxidant/anti-oxidant imbalance in patients with chronic renal disease is an important approach for the reduction of the risk for those patients to develop cardiovascular disorders and renal failure (Massy and Nguyen-Khoa 2002; Locatelli, Canaud *et al.* 2003).

Ang II is a potent stimulator of oxidative stress and RAS-blocade can already have an anti-oxidant effect (Calo *et al.* 2002).

Plasma homocysteine as well as blood glutathione are associated with CRF and hypertension (Annuk, Fellstrom et al. 2001; Muda *et al.* 2003). It is accepted that plasma total homocysteine elevated levels may be reduced by supplementation with folic acid or combinations of folic acid, vitamin B_{12}, and vitamin B_6. Folic acid is necessary for homocysteine metabolism, and therapy with folic acid reduces highly elevated plasma total homocysteine concentrations in CRF patients, although seldom to the normal (Dierkes *et al.* 1999; Sunder-Plassmann *et al.* 2000; Kaplan *et al.* 2001; Elian and Hoffer 2002). Supplementation with vitamin B_{12} resulted in total homocysteine reduction among CRF patients, although other investigators find no effect (Hyndman *et*

al. 2003). Supposedly, the efficacy of vitamin B_{12} and folate supplementation on plasma total homocysteine levels may depend on individual genotype (Nakamura *et al.* 2002).

Adequately designed antioxidant administration as an adjuvant therapy may have clinical impact for reducing cardiovascular complications in chronic renal failure (Tremblay *et al.* 2000). It has been showed that high-dose vitamin E supplementation for longer period of time could be beneficial for ESRD patients (Boaz *et al.* 2000).

2.3.7. Exercise therapy as an important part of complex rehabilitation

Among non-pharmacological approaches, aerobic exercise could be advised for CRF patients more often to increase their general conditioning and stabilise the renal function for longer period of time (Painter *et al.* 1999; Kouidi 2002). Permanent physical inactivity is one of the major risk factors of atherosclerosis. CRF patients have usually limited exercise tolerance (DePaul *et al.* 2002) and diabetic and elderly patients have a significantly lower result than the rest of the patients (Wiberg 2003). Exercise therapy is an important part of complex rehabilitation for CVD patients (Shephard and Balady 1999). As patients with chronic renal disease are considered in the highest risk group of premature atherosclerotic cardiovascular events, all beneficial cardiovascular rehabilitation strategies should be included in their management, in addition to the renoprotective pharmacological therapies to retard the development of risk factors for CVD and possibly slow the progression of RF. Preventive measures should be undertaken, encouraging patients to increase their physical activity and optimise their functional capacity as early as possible.

Exercise training has been shown to have a positive influence on physical capacity (Clyne *et al.* 1991; Death 1999), hypertension (Petrella 1998), left ventricular function (Deligiannis *et al.* 1999), lipid and glucose metabolism (Tran and Weltman 1985; Laaksonen *et al.* 2000), OxS and inflammation status (Arak-Lukmann 2002; Pihl *et al.* 2003), anemia (Painter *et al.* 2002) and quality of life (Painter *et al.* 2000) in CRF patients and in patients on renal replacement therapy (Boyce *et al.* 1997; Fitts *et al.* 1999). Moderate exercise has proved to possess antioxidative influence especially with a combination of dietary measures (Roberts *et al.* 2002). Important questions in the progression prevention strategies of chronic renal disease patients are mode, intensity, frequency, duration, and regularity of exercise (Painter 1994; Konstantinidou *et al.* 2002; Sietsema *et al.* 2002).

2.3.7.1. Mode of exercise

There are various suggestions for exercise therapy; the more traditional of them being walking, stock-walking, jogging, cycling or low and moderate impact aerobics programmes. Exercise should be dynamic, enjoyable, easily accessible and without adverse effect for optimal impact. Generally, exercise training is being recommended to patients as a complementary therapeutic modality held in a rehabilitation centre under the supervision of a physiotherapist or as a good, counselled, home exercise programme. The exercise prescription must include measures to minimise both cardiovascular and musculoskeletal risk. An individualised programme is needed to encourage patients to increase their physical activity.

The chronic renal failure, and pre-dialysis, population is old and the worsening of physical fitness is more pronounced among older individuals (Johansen *et al.* 2000). Skeletal muscle weakness and fatigue causes poor functional ability, especially when the renal dysfunction becomes aggravated. Regular exercise, already in the pre-dialysis stage, individually programmed by a specially trained physiotherapist, will further ameliorate the condition of renal patients. The chosen mode of exercise should be enjoyable for the individual patient and simple to carry out in order to maximise compliance. Exercising should bring by a joyful experience.

Among a wide variety of aerobic training possibilities, aquatic exercise is a novel approach in CRF patients' rehabilitation programmes. Water-based exercise could allow older, obese and not as well motivated patients to more easily gain all the advantages of land-based exercise. Non-swimming aquatic exercises have shown a beneficial effect, particularly useful in patients with orthopaedic problems (Ruoti *et al.* 1994). Water immersion causes increase in renal blood flow and contributes to the lowering in renal sympathetic nerve activity, renal vascular pressure and decrease in plasma renin activity (Epstein 1992; Becker and Cole 1998). Some experimental studies have shown that exercise in a water environment could improve renal functioning and even slow the progression rate (Heifets, Davis et al. 1987; Osato, Onoyama et al. 1990). Land-based exercise studies have not yet shown a benefit for renal function either in clinical (Eidemak, Haaber et al. 1997) or in experimental studies (Averbukh, Marcus et al. 1992; Bergamaschi, Boim et al. 1997).

It has been investigated and summarised by Epstein (Epstein 1992) that aquatic immersion influences renal function positively: plasma renin activity is reduced contributing to renal vascular pressure and sodium excretion. In CRF patients and hypertensive individuals, sympathetic tone is consistently raised (Orth, Amann et al. 2001; DiBona 2002). Therefore, the aquatic environment is an ideal one for mitigation of sympathetic over-activity (Grossman *et al.* 1992; Ikeda *et al.* 1994). It is known that aquatic exercise lowers blood pressure in hypertensive patients (Tanaka *et al.* 1997).

Blood flow during exercise is preferentially directed to working muscle, and away from other central organs like the kidney (Clorius *et al.* 1996). Distribution of blood flow is influenced by sympathetic arterial vasoconstriction and is pronounced in hypertensive individuals (Clorius, Haufe et al. 2002). Aquatic immersion creates physiologically non-invasive effects on renal regulatory systems, as has been published by Epstein: renal blood flow increases upon immersion. Water immersion *per se* abates the renal vasoconstriction during exercise. Orthostatic and renal vasoconstrictive risks of land-based exercise can be avoided when exercising in an aquatic environment.

2.3.7.2. Intensity of exercise

The intensity of exercise may usually range from 40 to 85 percent of functional aerobic capacity (VO_2max), but it should be low or moderate intensity (from 40 to 60 percent of VO_2max) for CRF patients. The intensity of aquatic exercise could be low in comparison with land-based exercise while, water immersion, with its influence, gives more effect for the effort (Becker and Cole 1998) and there is a shorter period needed for recovery from aquatic exercise (Weber-Witt 1994). It is essential that the risks of exercise must be assessed along with potential benefits. The most serious inherent risk of exercise, in the pre-dialysis population, could be cardiovascular complications. These could be avoided with a provision of a prolonged warm-up and exercise adaptation period and time allowance for adequate cool-down. If the exercise starts at low intensity, the associated risk for kidney patients should be minimal. For most of the CRF patients, the risk benefit ratio will fall in favour of exercise, compared to the majority of patients exposed to greater risk by not exercising.

2.3.7.3. Duration and content of exercise

Exercise conditioning consists of three phases:

1. Warm-up for 5 to 10 minutes. Warm-up exercises consist of stretching, flexibility movements and aerobic activity that gradually increase the heart rate. The gradual increment in blood flow minimises the risk of exercise-related cardiovascular complications.
2. Conditioning phase lasts for 10 to 20 minutes involving aerobic activity.
3. Cool-down period for 5 to 10 minutes. The cool-down time includes low-intensity exercise and permits a gradual recovery from the previous phase. Omitting the cool-down period results in a transient decrease in venous return, in the time-period when oxygen consumption is still high. It is better to make the warm-up and cool-down periods longer in renal disease patients and to increase the duration rather than intensity (Clorius, Mandelbaum et

al. 1996). Exercise should be monitored and supervised to prevent cardiac complications.

2.3.7.4. Frequency and regularity

Long-term observational studies, in preventive cardiology, show that those individuals who exercise regularly have significantly less cardiovascular complications (Clarkson *et al.* 1999; Higashi *et al.* 1999; Smith *et al.* 1999; Marlowe 2001).

Increased physical activity should be fostered in such ways that it becomes a routine part of the medical therapy early in the treatment period and in the mindset of the patient who then strives for self-improvement. Exercise should be regular, but even 2–3 times per week produces a beneficial effect (Suh *et al.* 2002), including a certain decrease of LPO and high sensitive CRP level. Prolonged low-intensity exercise has a substantially greater effect on renal hemodynamics in hypertensive renal failure patients than in healthy controls (Svarstad, Myking et al. 2002).

The importance of regular physical activity in lifestyle changes in patients with CRF should not be overlooked.

2.3.8. Education and management of the psychosocial problems

Various studies of the benefits of patient education programmes have shown that educated patients have a reduced incidence of emergency dialysis compared with control patients (Binik *et al.* 1993; Golper 2001). Education of patients early in the course of CRF offers many potential benefits for patients and healthcare professionals, including improved treatment outcomes, reduced anxiety, greater prospect for continued employment, improved timing for the start of dialysis, and a greater opportunity for intervention to delay disease progression (Bakewell *et al.* 2002). A 2-year trial with hypertensive patients in Finland showed beautifully that systematic lifestyle counselling can lower blood pressure levels (Kastarinen *et al.* 2002).

Individual or group psychotherapy and sometimes pharmacotherapy can be beneficial (Barrett 2003). Social, financial, and other counselling methods should be provided as necessary, together with patient education, regarding treatment, including modalities and other aspects of care. The social impact of these efforts primarily will be on the patient's quality of life, and secondarily, on family members and friends. Quality of life depends on many factors, including modality of treatment and adequacy of dialysis. In patients who are employed, efforts should be made to maintain their employment status and

social co-worker counselling should be provided for unemployed patients (Oberley, Sadler et al. 2000).

Each patient's condition should be taken into account individually when suggesting complex therapies. Careful management of the patient, in the pre-dialysis period, in the most appropriate setting for the individual patient's needs, would best achieve this. Vocational counselling as an important part of non-pharmacological treatment could not remain under-valued.

2.3.9. Summary

End-stage renal disease (ESRD) poses a large and growing morbidity, mortality, and financial burden (Blagg 1994). Almost all patients reach ESRD as a result of chronic progressive many years lasting conditions, particularly diabetic nephropathy, hypertensive-vascular renal disease, and glomerular disorders.

Therefore, both medicament and non-medicament strategies preventing progression of RF should be united — nutritional counselling, cessation of smoking, good blood pressure control etc. Avoidance of further renal insults such as the use of nephrotoxic drugs and radiographic contrast can slow the decline of renal function. Rehabilitation of patients with CRF should encompass all aspects of the patient's well being and include vocational, physical, and medical therapies. Family physicians play an important role in early recognising patients with potential for renal failure to improve the outcomes. Patients at risk merit regular renal assessment with serum creatinine tests and urine analysis for existing proteinuria. Population screening is even advisable (Briganti *et al.* 2003). Protective therapy may have the greatest impact if initiated early in the course of renal failure development, before the plasma creatinine concentration exceeds 132 to 176 μmol/l. To achieve a maximal efficacy, reno-protective and cardio-protective treatment has to be initiated as early as possible in the course of renal failure (Muirhead 2001). Because of its complexity, the integrated combined nephroprotective and cardioprotective therapy requires early and sustained guidance by a nephrologist throughout the whole CRF period (Avorn *et al.* 2002). Timely involvement of specialised rehabilitation team (dietary specialist, physiotherapist, social co-worker) could be beneficial, especially in pre-dialysis state. Systematic vocational counselling and encouraging of participation in an exercise-conditioning programme could bring important benefit from the public health point of view, that needs further investigations.

Although, classes of drugs that inhibit ACE or block angiotensin II receptors are widely used antihypertensive medicines in therapeutic management of hypertension and chronic renal diseases, recent meta-analysis in hypertensive subjects have shown that the comparison of various antihypertensive therapies still needs more investigations (Angeli *et al.* 2004) under the basis of indicative biochemical parameters. Less is known, how RAS-blocking therapy influences

OxS status in kidney and could it be superior to RAS independent beta-blocking therapy in protecting the kidney tissue from lipid peroxidation.

On the other hand, different non-pharmacological manipulations for more systemic therapy could be included to the complex of renoprotective therapy, such as water-based exercise for CRF patients. Although, the safety and the possible benefits of aquatic exercise to the renal function of the CRF patients are not yet been investigated.

3. AIMS OF THE STUDY

The study is aimed at elucidating the role of medicamentous and non-medicamentous treatment in the progression preventive strategies in chronic renal failure and hypertension.

Accordingly, the specific objectives of the study were:

1. To study the impact of anti-hypertensive treatment with an angiotensin II receptor antagonist (losartan) and a beta-blocker (atenolol) on blood pressure, renal function, oxidative stress status and morphological changes in the kidney tissue in an experimental model of chronic renal failure and hypertension (remnant kidney).
2. To determine the impact of implementation of the regular long-term (12 weeks) water-based aerobic conditioning on the renal and cardio-respiratory functional indices and on the oxidative stress status in those patients with mild and moderate chronic renal failure.

4. PART I:
The impact of anti-hypertensive treatment with renin-angiotensin system blocking agent (losartan) and beta-blocking agent (atenolol) on blood pressure, oxidative stress status and renal parameters in experimental chronic renal failure (Paper I)

4.1. Materials and methods

4.1.1. Experimental design

Male Wistar rats were subjected to a subtotal (5/6) nephrectomy (NPX) as previously described (Ots, Mackenzie et al. 1998) at week (wk) 0, at approximately 8 wks of age, rats weighing 262–280 g were anesthetized with intraperitoneal methohexital sodium, 5 mg per 100 g body weight. Renal ablation was then accomplished by right nephrectomy and selective ligation of extrarenal branches of the left renal artery in such a way that approximately 2/3 of the left kidney was infarcted.

Fifty-five rats were randomized after the surgery and divided into six groups matched for age and body weight at wk 0 and studied during 2 and 4 wks: NPX-2wk (n=8), NPX-4wk (n=7), NPX+Losartan (Los)-2wk (n=10), NPX+Los-4wk (n=10), NPX+atenolol (At)-2wk (n=10), NPX+At-4wk (n=10). Body weight was measured every week for the duration of the study. Systolic blood pressure (SBP, mmHg) was measured weekly by the tail-cuff manometer (Harvard Apparatus, USA) in awake pre-warmed rats. The urine was collected for 24 hours (h) using metabolic cages at wk 2 and 4, for determination of urine creatinine (U-Crea, μmol/l), and proteinuria (Uprot, g/24h) that were measured with Hitachi 912 Analyser. Blood was collected from the aorta for serum creatinine (S-Crea, μmol/l) and was measured using Hitachi 912 Analyser.

Treatment with AT_1RA (losartan, 180 mg/l) and beta-blocking agent (atenolol, 750 mg/l) was added to the drinking water and started immediately after the operation. Drug solutions were freshly prepared immediately prior to use.

After the study period rats were anesthetised using methohexital sodium (50 mg per 100g body weight) and the blood collected from the aorta for biochemical and OxS tests. The remnant kidneys were removed and a piece from the cortex for the OxS tests was taken and remaining tissue fixed in 10% buffered formaldehyde. Paraffin sections of coronal slices, through the pelvis of the remnant kidney, were cut at a 4 mm thickness and stained using the periodic acid-Schiff (PAS) and Masson's trichrome methods.

4.1.2. Oxidative stress indices

We measured following parameters: Products of lipid peroxidation, malondialdehyde and 4-hydroxyalkenals together (LPO) in kidney cortex tissue and in serum; markers of antioxidant status: concentrations of total glutathione (TGSH) including reduced (GSH) and oxidized forms (GSSG) in kidney cortex tissue and in serum; markers of the common OxS based load of the body: 8-isoprostanes in fresh urine. The procedures met the criteria and principles described previously (Halliwell and Gutteridge 1999). Products of lipid peroxidation (LPO): malondialdehyde and 4-hydroxyalkenals together were measured in renal cortex tissue homogenate (LPO, pmol/mg protein) and in serum (LPO, ng/ml) by colorimetric assay for lipid peroxidation using the manufacturer kit LPO-586^{TM} (Bioxytech®). Concentrations of total glutathione (TGSH) including reduced (GSH) and oxidised forms (GSSG, all in μM) were assessed by an enzymatic method as described previously (Griffith 1980). The blood was de-proteinated by 10% solution of metaphosphoric acid (MPA) in water, adding an equal volume of MPA to the blood (Cayman Clinical Company, Ann Arbor, MI, USA).

Fresh urine was collected at week 2 and 4. Samples were stored at –20°C until analyzed. Isoprostanes in fresh urine were measured by the ELISA technique using the manufacturer kit (Bioxytech®). The urine isoprostane data were expressed in ng per mg creatinine.

4.1.3. Morphologic studies

Sections from each kidney were studied morphologically for evidence of focal-segmental glomerulosclerosis (FSGS), defined as glomeruli showing evidence of segmental or global collapse of capillaries with or without associated hyaline deposition and adhesions of the capillary tuft to Bowman's capsule.

The extent of FSGS was expressed as a percentage of the total number of glomeruli counted (>50/section).

The presence of interstitial fibrosis (IF) was measured in trichrome stained sections from each kidney and was graded according to the following scale: 0 – no evidence of interstitial fibrosis; 1 – <25% involvement; 2 – 25–50%; 3 – >50%.

4.1.4. Statistical analysis

Data were collected at baseline and after 5/6 NPX in rat groups at wk's 2 and 4. Data are presented as mean values ± SD. Data were analyzed by one-time ANOVA with the Tukey-Kramer test for comparisons significant at the 0,05 level or repeated ANOVA measures with post-hoc testing as appropriate using

the commercially available statistical package SAS. Co-relations were assessed using a one-sample *t* test for a correlation coefficient. The null hypothesis was rejected at $p < 0.05$.

4.2. Results

4.2.1. Blood pressure

Average levels of SBP in all treated groups were significantly lower than untreated animals ($p<0.05$). There were no differences in mean SBP among losartan- and atenolol-treated groups (Table 1).

Table 1. Mean systolic blood pressure (SBP)

Groups	Untreated-2wk	Losartan-treated-2wk	Atenolol-treated-2wk	Untreated-4wk	Losartan-treated-4wk	Atenolol-treated-4wk
SBP mmHg	143.0±4.3	100.0±1.0*	92.5±3.1 #	154.0±4.0	90.0±2.7 *	86.9±5.8 #

Values are mean ± SD. wk – week; *$p < 0.05$ Losartan-treated vs. untreated at corresponding wk; #$p < 0.05$ Atenolol-treated vs. untreated at corresponding wk

4.2.2. Oxidative stress status

Oxidative stress indices in the kidney tissue, in urine and in blood are presented in Table 2, 3 and 4, respectively.

Table 2. Indices of oxidative stress in kidney tissue after 2 and 4 weeks (wk): lipid peroxidation products (LPO), oxidised glutathione (GSSG), reduced glutathione (GSH) and glutathione redox ratio (GSSG/GSH)

Groups	Untreated 2wk	Losartan-treated 2wk	Atenolol-treated 2wk	Untreated 4wk	Losartan-treated 4wk	Atenolol-treated 4wk
LPO pmol/mg protein	0.202±0.01	0.151±0.01*	0.178±0.03	0.185±0.02	0.134±0.02*¤	0.191±0.09
GSSG μmol/ mg protein	1.6±0.4	1.3±0.2¤	0.7±0.1	1.6±0.2	2.8±1.0¤	0.9±0.1
GSH μmol/ mg protein	11.0±2.9	13.3±2.6 ¤	6.2±1.5	7.1±2.4	14.4 ± 4.4 ¤	5.5±1.0
GSSG/GSH	0.322±0.117	0.149±0.031*	0.246±0.115	0.399±0.133	0.354±0.080	0.220±0.031

Data are mean±SD; *$p < 0{,}05$ losartan-treated *vs*. untreated at corresponding wk; ¤ $p < 0{,}05$ losartan-treated *vs* atenolol-treated at corresponding wk

Losartan-treatment significantly suppresses LPO products (malondialdehyde and 4-hydroxyalkenals together) in the renal cortex tissue already in two weeks after treatment. At week 4, the level of LPO remains significantly lowered in losartan-treated rats compared with the atenolol or untreated animals (Table2, Fig.4).

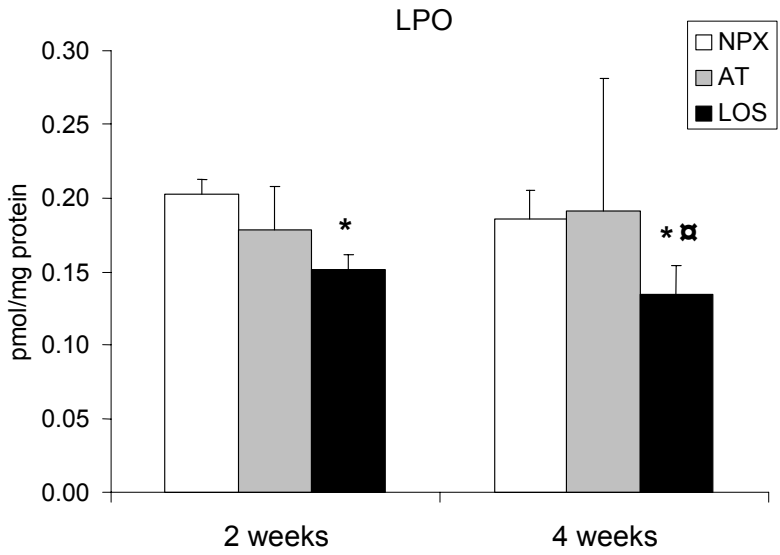

Figure 4. Lipid peroxidation (LPO) in the renal cortex tissue.
* $p < 0.05$ Losartan-treated vs. untreated at corresponding week,
¤ $p < 0.05$ Losartan-treated vs atenolol- treated at corresponding week
LOS — losartan-treated, AT — atenolol-treated, NPX — untreated groups

The level of the reduced glutathione (GSH, a cellular principal antioxidant) in losartan-treated rats was significantly higher compared with atenolol-treated animals (Table 2 and Fig.5). The glutathione redox ratio (GSSG/GSH) in the kidney tissue was significantly lower in losartan-treated rats by week 2 compared with untreated rats.

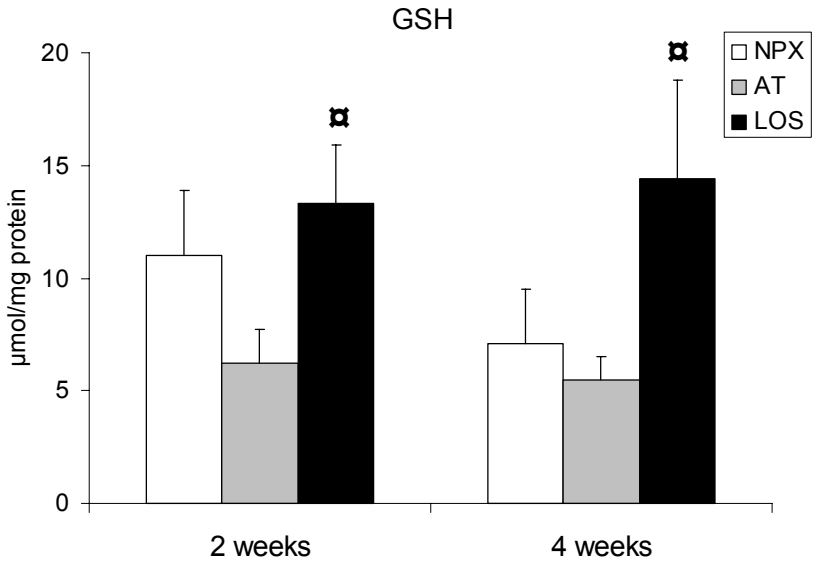

Figure 5. Reduced glutathione (GSH) in the renal cortex tissue.

* $p < 0,05$ Losartan-treated vs. untreated at corresponding week,
¤ $p < 0,05$ Losartan-treated vs atenolol-treated at corresponding week
LOS — losartan-treated, AT — atenolol-treated, NPX — untreated groups

Losartan-treatment diminished the excretion of isoprostanes by week 4 whereas with atenolol-treatment a further increase occurred (Table 3).

Table 3. Indices of oxidative stress in urine after 2 and 4 weeks (wk): Isoprostanes (ISO)

Groups	Untreated 2wk	Losartan-treated 2wk	Atenolol-treated 2wk	Untreated 4wk	Losartan-treated 4wk	Atenolol-treated 4wk
ISO ng/mg creat	2.95±0.58	3.74±1.25	3.41±1.35	2.72±1.19	1.81±0.55 ¤	6.37±2.9 #

Data are mean±SD. ¤ $p < 0,05$ losartan-treated vs atenolol- treated at corresponding wk
# $p < 0,05$ Atenolol-treated vs. untreated at corresponding wk

The data of blood samples are expressed in Table 4. Treatment with both drugs was not able to suppress the serum LPO at week 2 and it even noticeably aggravated systemic LPO compared with untreated animals. A small further increase of LPO was noticed in both losartan-treated and atenolol-treated groups by week 4. The glutathione redox ratio was significantly lower in

losartan-treated animals at week 4, compared with atenolol-treated, the smallest redox ratio was found in untreated animals.

Table 4. Indices of oxidative stress in blood after 2 and 4 weeks (wk): lipid peroxidation products (LPO), oxidised glutathione (GSSG), reduced glutathione (GSH), glutathione redox ratio (GSSG/GSH)

Groups	Untreated 2wk	Losartan-treated 2wk	Atenolol-treated 2wk	Untreated 4wk	Losartan-treated 4wk	Atenolol-treated 4wk
LPO ng/ml	0.586±0.04	0.910±0.03*	0.997±0.11#	0.954±0.06	1.205±0.05	1.080±0.14
GSSG μM	159.0±18.5	159.0±17.8	159.0±12.7	172.3±17.4	159.0± 17.8	159.0±9.4
GSH μM	622.1±70.3	475.0±40.6*	555.7±101.0	823.2±80.3	398.2±47.9*¤	182.3±14.4
GSSG/GSH	0.322±0.051	0.441±0.064	0.325±0.066	0.208±0.034	0.452±0.060¤	0.600±0.040

Data are mean±SD *p < 0,05 losartan-treated vs. untreated at corresponding wk; ¤ p < 0,05 losartan-treated *vs*. atenolol-treated at corresponding wk; # p < 0,05Atenolol-treated *vs*. untreated at corresponding wk

4.2.3. Renal functional parameters and body weight

Therapy significantly reduced UprotV both in losartan and atenolol groups compared with untreated animals. At week 2, the mean UprotV was significantly lower in the losartan-treated group than in the atenolol-treated group, but there were no significant differences among losartan- and atenolol-treated groups by week 4. Mean S-Creat was significantly lower in treated groups at week 4 compared with untreated animals ($p<0.05$). There were no differences in mean S-Creat among losartan- and atenolol-treated groups. There were no significant differences in body weights among the studied groups, at any point of time (Table 5).

Table 5. Body weight (BW), urine protein excretion rate (UprotV), and serum creatinine (S-Creat) after 2 and 4 weeks (wk)

Groups	Untreated 2wk	Losartan-treated 2wk	Atenolol-treated 2wk	Untreated 4wk	Losartan-treated 4wk	Atenolol-treated 4wk
BW g	283.0 ± 3.0	305.0 ± 5.0	311.0 ± 7.0	284.0 ± 6.0	303.0 ± 9.0	329.0 ± 6.0
UprotV mg/24 h	34.1 ± 6.4	17.4 ± 9.0 * ¤	23.2 ± 2.4 #	47.2 ± 10.4	19.4 ± 1.8*	22.3 ± 2.4 #
S-Creat µmol/l	105.3± 5.6	107.6 ± 5.2	99.5 ± 4.7	104.7 ± 4.6	93.3 ± 2.9 *	92.9 ± 2.8 #

Values are mean ± SD; * $p < 0,05$ losartan-treated vs. untreated at corresponding wk; ¤ $p < 0,05$ losartan-treated vs atenolol-treated at corresponding wk; # $p < 0,05$ atenolol-treated vs. untreated at corresponding wk

4.2.4. Morphologic findings

Less FGSG was found in the remnant kidneys of losartan-treated animals (2.3±2.3) compared with atenolol-treated (4.0±1.3) and untreated controls (6.4±5.5) at week 4. The IF scores in both losartan- (1.0±0.1) and atenolol-treated (0.9±0.3) animals were lower compared with untreated controls (2.0±0.0) ($p<0.05$).

4.3. Discussion

In the experimental part of the study, we evaluated the anti-OxS action of two anti-hypertensive agents, an AT_1RA (losartan) and a beta-blocker (atenolol) in the early stadium of chronic progressive renal failure. Both treatments lowered blood pressure and proteinuria to a similar extent during the study period. However, the glomerulosclerosis index was smallest in losartan-treated animals. Renal diseases progress to end-stage via focal and segmental glomerular sclerosis, independent of the initial cause. After renal mass reduction, the remaining nephrons undergo functional as well as structural hypertrophy, glomerular and systemic hypertension develops (Hostetter, Olson et al. 2001). The segmental sclerotic lesions that develop in remnant glomeruli of rats after subtotal nephrectomy (5/6NPX) resemble those seen in a variety of human chronic renal diseases. This remnant kidney model is used in our study to evaluate the dynamics of local and generalised OxS parameters in the early period of experimental CRF.

Angiotensin II (Ang-II) plays the central role in the development of the pathogenic disturbances (Weiss *et al.* 2001). Experimental and clinical studies

indicate that RAS blockers slow the rate of the progression of renal injury resulting from kidney diseases of diverse aetiologies.

Ang-II is undoubtedly related to OxS induction (Gonzales *et al.* 2002) and RAS blockade manipulation modulates the OxS status. Effects of RAS blockers on the OxS parameters in different mediums (blood, tissue homogenate, urine) have been previously studied in various experimental CRF models (Ha and Kim 1992) (Shou *et al.* 1997; Verbeelen *et al.* 1998; Gurer *et al.* 1999; Kedziora-Kornatowska 1999; Onozato *et al.* 2002; Tesar *et al.* 2002; Bayorh *et al.* 2004) and in human studies (Donmez, Derici et al. 2002; Agarwal 2003).

Several studies have shown beneficial effects of beta-adrenergic receptor blockade on the rate of the progression of renal failure (Brooks *et al.* 1993; Rodriguez-Perez *et al.* 1997; Van den Branden *et al.* 1997). However, the RENAAL study proved the priority of the angiotensin receptor type 1 antagonist (AT_1RA), losartan, in renoprotective medication (Brenner, Cooper *et al.* 2001). The LIFE study pointed that losartan is superior in reducing cardio-vascular events and mortality (Kjeldsen *et al.* 2002). There are different data whether RAS blockade can alter the grade of OxS in chronic progressive kidney diseases. Recent studies have shown the presence of systemic OxS in hypertensive individuals (Nemeth *et al.* 2001; Turi *et al.* 2003). In addition, the alteration of systemic and cellular oxidative stress is still open. Due to these reasons we investigated changes of both tissue and blood oxidative stress using two anti-hypertensive agents, an AT_1RA (losartan) and a beta-blocker (ate-nolol). We assessed their suppressing effects on the systemic and cellular OxS indices in after 5/6 nephrectomy (5/6NPX) in the early stages (at weeks 2 and 4) of experimental CRF comparing to untreated controls.

Despite the similar effect on blood pressure and renal parameters the LPO and reduced glutathione levels in the renal tissue of the losartan-treatment group were significantly better than in the atenolol-treatment group (Fig.6). This suggests that the local anti-oxidant action blocks the very high activity of tissue RAS in the insured kidney. We found that the RAS blockade with losartan already significantly diminishes LPO in renal tissue level in the early stages of experimental CRF, at week 2, having declining tendency further at week 4, when the difference between the atenolol-treated and losartan-treated groups was found to be highly significant. These results confirm the previous ones which have demonstrated that, in blunting Ang-II action, there is a decrease in OxS (Welch and Wilcox 2001).

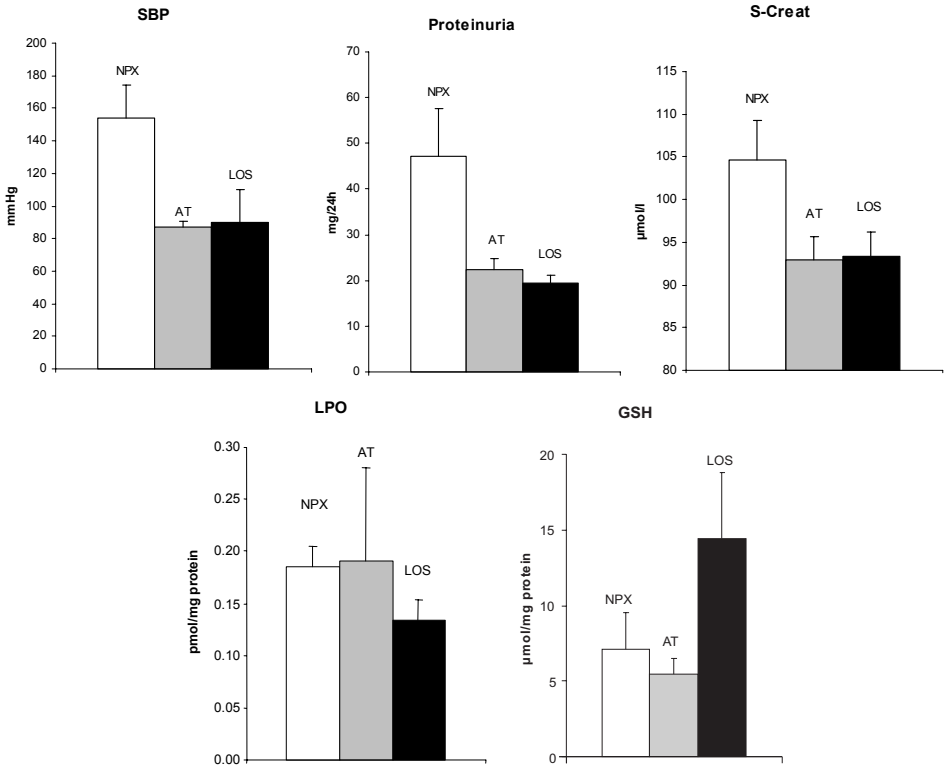

Figure 6. Systolic blood pressure (SBP), proteinuria, serum creatinine (S-Creat), lipid peroxidation (LPO) and reduced glutathione (GSH) after 4 weeks of study period. LOS — losartan-treated, AT — atenolol-treated, NPX — untreated groups

Reduced glutathione values showed that its synthesis was higher during losartan-treatment, but depressed in atenolol-treated rats. That points to better protection by losartan against pathological oxidation compared to atenolol. Evidently, the use of the RAS blocking agent in our study ameliorates the anti-oxidant status in renal tissue of 5/6NPX rats, probably providing local anti-oxidative impact and this was not achieved with the atenolol-treatment. In the condition of elevated oxygen radicals' production, losartan was able to blunt the deleterious effect of metabolic changes in the kidney.

Progression of oxidative stress caused by (5/6NPX) in remnant kidney tissue was significantly suppressed only by the losartan treatment. Despite a similar blood pressure lowering effect, both the LPO level (indices of lipid peroxidation) and reduced glutathione (a principal cellular antioxidant) in the renal tissue of the losartan-treated group were significantly better than in the atenolol-treated group (Fig.6). It seems that the effect of losartan is GSH-mediated but not the redox-ratio-mediated, as this ratio, in the renal tissue, showed no significant difference between both treatment groups in this study period (I).

Systemic lipid peroxidation (LPO) is significantly increased in rats after 5/6 NPX. In our study, LPO was elevated in all groups without blunting the action of anti-hypertensive drugs. It is of particular interest that losartan treatment lowered renal tissue but not systemic LPO at week 2 and 4. Moreover, in both treatment groups the LPO value in plasma was significantly higher than in untreated controls at week 2, and remained higher, although not significantly, at week 4 where the atenolol-group showed an even lower level than the losartan-group. The discrepancies between tissue and plasma LPO values in the early period of CRF are difficult to discuss. It is evident that the RAS blockade in the kidney influences local tissue LPO to a much greater extent than in blood, at least in the very early stage of experimental CRF. It is possible that the short-term follow up did not permit the observation of modifications showing a clear-cut positive action by losartan.

Serum glutathione levels were markedly elevated after 5/6 NPX. The highest value of serum glutathione was found in untreated animals. On the other hand, reduced glutathione levels in the blood at week 4 were significantly higher in losartan-treated animals, compared with the atenolol-treatment, which could be interpreted as better anti-OxS action of losartan at the systemic level. Losartan-treatment prevented the decrease of GSH levels to the contrary situation of atenolol-treatment.

Thus, losartan-treatment suppresses the development of pathological renal cellular OxS but not the blood one in the early period of chronic renal failure. Its cellular effect seems to be GSH-mediated. Atenolol-treatment also interferes with the glutathione system as it decreases both GSSG and GSH in the renal tissue in our study (I).

In summary, losartan enables the controlling of the progression of OxS in the kidney tissue level during the early stages of experimental chronic renal failure. This finding may partly explain the renoprotective effect of angiotensin II receptor antagonists.

Urinary isoprostanes are markers of the common oxidative stress-based load of the body. Thus, the assay of urinary isoprostanes gives useful information about changes in systemic OxS. Both treatments (losartan, atenolol) induced some elevation of isoprostanes at week 2, which can be observed in parallel with the systemic LPO status that corresponds with the data of Tesar *et al*. in the adriamycin-induced nephritic syndrome model (Tesar, Zima et al. 2002). Urinary isoprostanes decreased in losartan-treated rats from 2 weeks to 4 weeks, in atenolol-treated rats a further increase occurred. It could be related to effects of anti-hypertensive agents on lipid peroxidation process in serum and thus probably in the filtered load. Both treatments (losartan, atenolol) induced elevation of urine isoprostanes at week 2; it is noteworthy that, considering the 4-week condition, the urinary isoprostanes level is lower in losartan-treated rats compared with untreated animals. At the same time the level of urinary isoprostanes is characterised by a further increase in atenolol-treated rats.

There were no major changes concerning the physiological and morphological parameters between the animals treated with AT_1RA or beta-blocker in 4-week study period, although the tendency of less glomerulosclerosis and interstitial fibrosis was noticed in the group treated with losartan. Losartan's renoprotective characteristics may be related to the anti-OxS action and lipid peroxidation decline, presumably due to RAS diminished activity in kidney. Our study showed that the measurement of LPO in kidney tissue gives valuable information in biochemical level; despite the similar effect of AT_1RA or beta-blocker on BP and proteinuria in 4-week period, the kidney tissue LPO was significantly lower only after AT_1RA-treatment.

5. PART II:
The impact of aquatic exercise on blood pressure, oxidative stress level, cardio-respiratory, renal and lipid parameters in those patients with chronic renal failure (Papers II; III; IV)

5.1. Patients

Twenty-six patients with mild to moderate progressive CRF participated in the study: seventeen in the exercise group, nine patients remained sedentary and formed the control group. Clinical characteristics of the patients at baseline are given in Table 6.

Table 6. Clinical characteristics of study patients at baseline (mean values±SD)

	Exercise group (n=17)	Control group (n=9)
Age (years)	52 (range 31–72)	48 (range35–65)
Gender, male/female	7/10	6/3
PeakVO_2 (ml/kg/min)	18.8±0.9	21.0±2.9
GFR (ml/min)	62.9±5.9	69.8±12.3
S-Crea (μmol/l)	141.8±11.7	154.4±23.4
Cys-C (mg/l)	1.7±0.2	1.7±0.3
SBP (mmHg)	147.5±4.5	147.8±5.7
DBP (mmHg)	87.4±2.4	90.2±3.0

No significant differences between parameters of study groups were found. Diagnoses of participating patients were the following: diabetes mellitus type I — 3, type II — 3, essential hypertension — 4, chronic glomerulonephritis — 15 patients, chronic pyelonephritis — 1. All patients had mild or moderate proteinuria and nobody was anaemic. 15 patients had mild cardiovascular problems (NYHA I–II). Medication was not changed during the rehabilitation programme. There was no dietary change; the patients followed their usual diet habits. Informed consent was obtained from all patients and the Ethics Review Committee on Human Research at the University of Tartu approved the study protocol. All data were collected at baseline and after the 12-week follow-up.

5.2.Methods

5.2.1. Stress test protocol

Cardio-pulmonary exercise testing was performed using the bicycle ergometer **"**Siemens 380"**.** The protocol began with resting data for 1 minute. The workload started at 40 watts (W) with increments of 10 W per minute until volitional fatigue, dyspnoea or other indications for stopping the test occurred. Recovery included 2 minutes of no-load cycling followed by a seated rest for 15 minutes. Functional indices of the cardio-respiratory system were measured continuously using an automated expired gas analyser (Oxycon Record, Erich Jaeger, 1993). Following cardio-respiratory parameters were taken at baseline and after 12-week follow-up: peak oxygen uptake (peak VO_2, ml/kg/min), peak oxygen pulse (VO_2, ml/kg/min), peak ventilation (l/min) and peak load (W). Resting blood pressure was measured in a sitting position before testing and after a 15 minutes recovery period.

5.2.2. Exercise conditioning

The study group exercised vertically in the pool with total immersion to the shoulder (at water temperature $+24^{o}$) twice a week for 12 weeks with sessions lasting 30 minutes, involving rhythmic movements for joints and body (aerobic exercise). These activities were supervised by a trained physiotherapist and based on a comprehensive plan by a physical specialist. The exercise program consisted of a 10-minute warm-up period with gentle stretching, a 10-minute cardiovascular segment of exercises with gradually increasing intensity and a 10-minute cooling down period with a final stretching time. The group all exercised at low-intensity (40–50% of their individual peak oxygen uptake heart rate). Heart rate (HR, b/min) was monitored with a sport-tester (Polar Electro) during exercising (max HR was taken after the most intense moment after gradually increasing the intensity exercise part). Blood pressure, both systolic and diastolic blood pressure (SBP, DBP, mmHg), was measured before (resting 15 minutes in sitting position) and after 15 min resting on completion of the training.

5.2.3. Markers of oxidative stress

Products of lipid peroxidation (LPO, ng/ml) malonaldehyde and 4-hydroxyalkenals together were measured in serum by colorimetric assay for LPO (Bioxytech® LPO-586^{TM}). Diene conjugates (DC, μM) were measured as described by Starkopf et al 1997 (Starkopf *et al.* 1997). Markers of antioxidant

status: concentrations of total glutathione (TGSH) included reduced (GSH) and oxidised forms (GSSG, all in μM) were assessed by an enzymatic method (Griffith 1980). Isoprostanes in fresh urine (ISO, ng/mg creat) were measured by the ELISA technique (Bioxytech®).

5.2.4. Plasma lipids and renal parameters

Blood samples were obtained via venopuncture fasting. Serum total cholesterol (S-Chol, mmol/l), triglycerides (Tg, mmol/l), HDL and LDL-cholesterol (mmol/l), serum- and urine creatinine (μmol/l) and urinary protein excretion (U-prot, g/24h) were measured using a Hitachi 912 Analyser. Glomerular filtration rate (GFR, ml/min) was calculated from endogenous creatinine using the Cockroft-Gault formula. Cystatin-C (Cys-C, mg/l) was measured by particle-enhanced turbidimetric assay (DAKO).

5.2.5. General health status

Patient-side subjective outcome of general health status was assessed in an interview, using one question: “How do you evaluate your general health status now?” It was characterised using numerical values from 1 to 10 and was interpreted as following: points 10–8 = good; points 7–4 = average; points 3–1 = poor.

5.2.6. Statistics

Group data are presented as means±SD. Differences between the initial and final values within the group were evaluated using the two-sample paired t-test for means. The $p < 0,05$ was accepted as statistically significant.

5.3. Results

5.3.1. Blood pressure and cardio-respiratory parameters

In the exercise group, a significant decrease in both SBP and DBP was noticed. Indices of cardio-respiratory reserve and physical capacity in the exercise group showed improvement in all parameters (Table 7). Peak oxygen pulse (ml/b/min±SD), peak ventilation (l/min±SD) and peak load (W±SD) were significantly improved when comparing data before and after the rehabilitation

programme. Mean peakVO_2 (ml/kg/min±SD) was also better, although not significantly. There were no significant changes in the control group.

Table 7. Values of cardio-respiratory parameters

	Exercise group at baseline	Exercise group after follow-up	Controls at baseline	Controls after follow-up
SBP (mmHg)	147±4.0	139±4.0*	148±6.0	147±9.0
DBP (mmHg)	87±2.0	84±2.0*	90±3.0	87±5.0
PeakVO_2 (ml/kg/min)	18.8 ±0.9	19.2±1.0	21.0±2.9	21.3±3.2
Peak O_2 pulse (ml/b/min)	11.1±0.6	13.3±1.2*	12.5±1.5	14.6±1.9
Peak ventilation (l/min)	51.3±2.7	55.7±2.1*	55.4±7.2	50.7±5.9
Peak load (W)	96.5±11.6	110.9±15.8*	127.8±12.4	124.4±15.3

*p<0.05 follow-up vs. baseline

5.3.2. Oxidative stress status

Oxidative stress parameters are presented in Table 8. The serum LPO level decreased and the reduced glutathione value increased significantly in the exercise group. Individual values of the glutathione redox ratio (GSSG/GSH) normalised in 16 out of 17 exercising patients, the group mean change was significant. There was no significant change in excretion of isoprostanes in urine.

There were no significant changes in OxS status in the control group.

Table 8. Values of lipid peroxidation products (LPO), diene conjugates (DC), total glutathione (TGSH), its oxidised (GSSG) and reduced (GSH) forms and redox ratio(GSSG/GSH) in serum and isoprostanes in urine (ISO)

	Exercise group at baseline	Exercise group after follow-up	Controls at baseline	Controls after follow-up
LPO (ng/ml)	1.51 ± 0.23	0.99±0.11*	0.99±0.06	1.35±0.15
DC (μM)	50.3 ± 4.0	46.5±3.7	53.3±4.6	48.2±5.0
TGSH (μM)	789.9 ± 53.3	790.0±49.9	844.4±113.5	648.1±125.0
GSSG (μM)	75.5 ± 12.1	56.8±9.4	63.6±5.9	40.4±4.6
GSH (μM)	751.2 ± 46.8	864.2±44.5*	869.1±44.3	607.9±123.6
GSSG/GSH	0.102 ± 0.014	0.068±0.011*	0.074±0.007	0.145±0.059
ISO(ng/mg creat)	1.67 ± 0.46	1.96 ± 0.27	1.80 ± 0.41	1.00 ± 0.04

*p<0.05 follow-up vs.baseline

5.3.3. Renal functional parameters

Proteinuria and Cys-C values diminished significantly in the exercise group, GFR had an ameliorating tendency. There was no significant change in the control group. Renal functional parameters are shown in Table 9.

Table 9. Values of renal functional parameters

	Exercise group at baseline	Exercise group after follow-up	Controls at baseline	Controls after follow-up
S-Crea (μmol/l)	141.8 ±11.7	135.0±10.4	154.4±23.4	178.4±34.3
GFR (ml/min)	62.9±5.9	67.1±7.0	69.8±12.3	66.3±13.2
Cys-C (mg/l)	1.7±0.2	1.4±0.1*	1.7±0.3	2.0±0.5
U-Prot (g/24h)	0.7±0.2	0.4±0.2*	1.4±0.3	1.5±0.3

*p<0.05follow-up vs. baseline

5.3.4. Values of body mass index and blood lipids

There was no change observed in the BMI of the group mean or among the individuals either in the exercise or in the control group. No significant change was observed in blood lipids (Table 10).

Table 10. Values of body mass index and blood lipids

	Exercise group at baseline	Exercise group after follow-up	Controls at baseline	Controls after follow-up
BMI (kg/m^2)	29.4±1.3	29.4±1.3	28.1±1.3	28.1±1.3
T-Chol (mmol/l)	6.4±0.2	6.1±0.2	6.3±0.6	6.0±0.5
HDL (mml/l)	1.3±0.1	1.3±0.1	1.2±0.1	1.4±0.2
LDL (mmol/l)	4.1±0.1	3.9±0.1	3.9±0.5	3.8±0.5
Tg (mmol/l)	2.3±0.2	2.2±0.2	2.8±0.8	2.4±0.5

5.3.5. General health status

In the general health-related evaluation of life quality of the exercise group there was a significant rise in the score: 6, 6 points before to 4, 5 points after ($p<0.05$), the mean value remained in the range “average”.

5.4. Discussion

The present study shows consistent with the data from other authors, that cardio-respiratory functional capacity of renal patients can be significantly improved in regular physical activity performance (Goldberg *et al.* 1983; Boyce, Robergs et al. 1997; Painter *et al.* 2002). Cardio-respiratory reserve and physical capacity indices were improved in our study exercise group; remained unchanged, even worsened, in sedentary control group. Peak VO_2, peak workload and peak ventilation are considered the variables that reflect exercise tolerance and usually improve after training (Fig. 7).

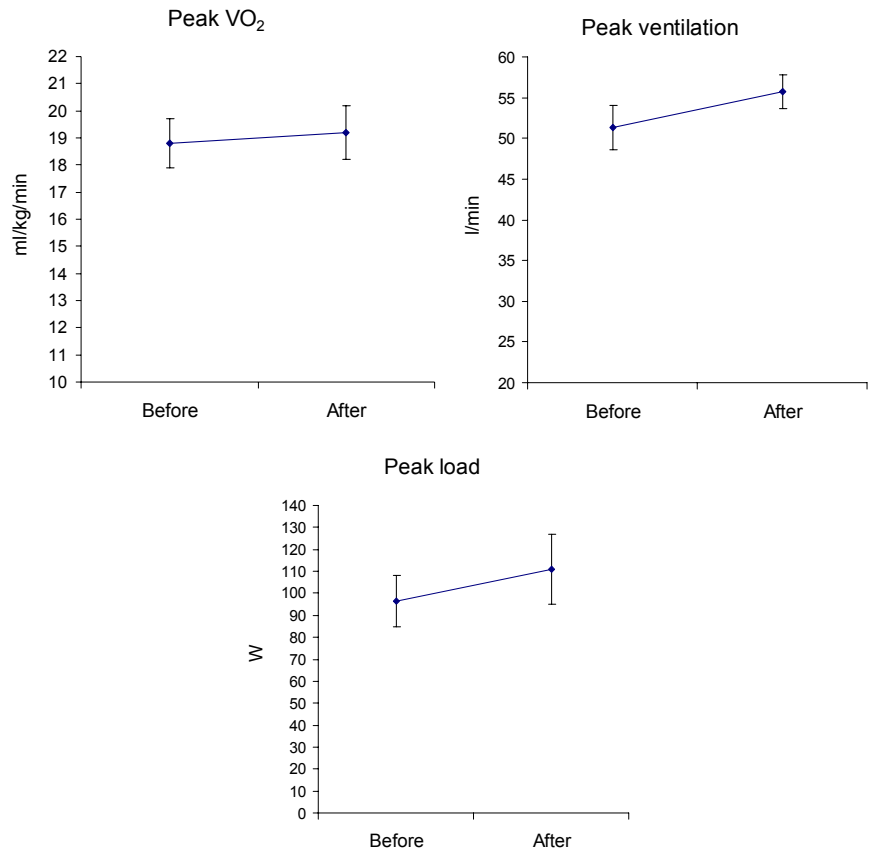

Figure 7. Peak VO_2, peak workload and peak ventilation before and after the regular 12-week aerobic water-based exercise.

Although there are no clear guidelines for exercise training for patients with renal disease, it has been emphasized that most of these patients can benefit from increased physical activity.

We chose the water-based exercise from the various suggestions for aerobic exercise therapy because the low-intensity exercise has been showed to be optimal for renal patients for an adequate response and the intensity of aquatic exercise could truly be low in comparison with land-based exercise while water medium gives more effect to the effort. Older, obese and less motivated patients gain in water all the advantages of land-based exercise more easily (Ruoti, Troup et al. 1994). The most important aspect for optimal impact is that the exercise should be enjoyable and relaxing for the individual patient.

In our study we obtained improvement in renal functional parameters: proteinuria diminished significantly (Fig. 8) and serum cystatin C decrease was reinforced by small GFR improvement (II, III, IV). This effect bears a resemblance to experimental results made previously in small animals. Interestingly, studies with uremic animals (Heifets, Davis et al. 1987; Osato, Onoyama et al. 1990) have shown that swimming exercise significantly reduced

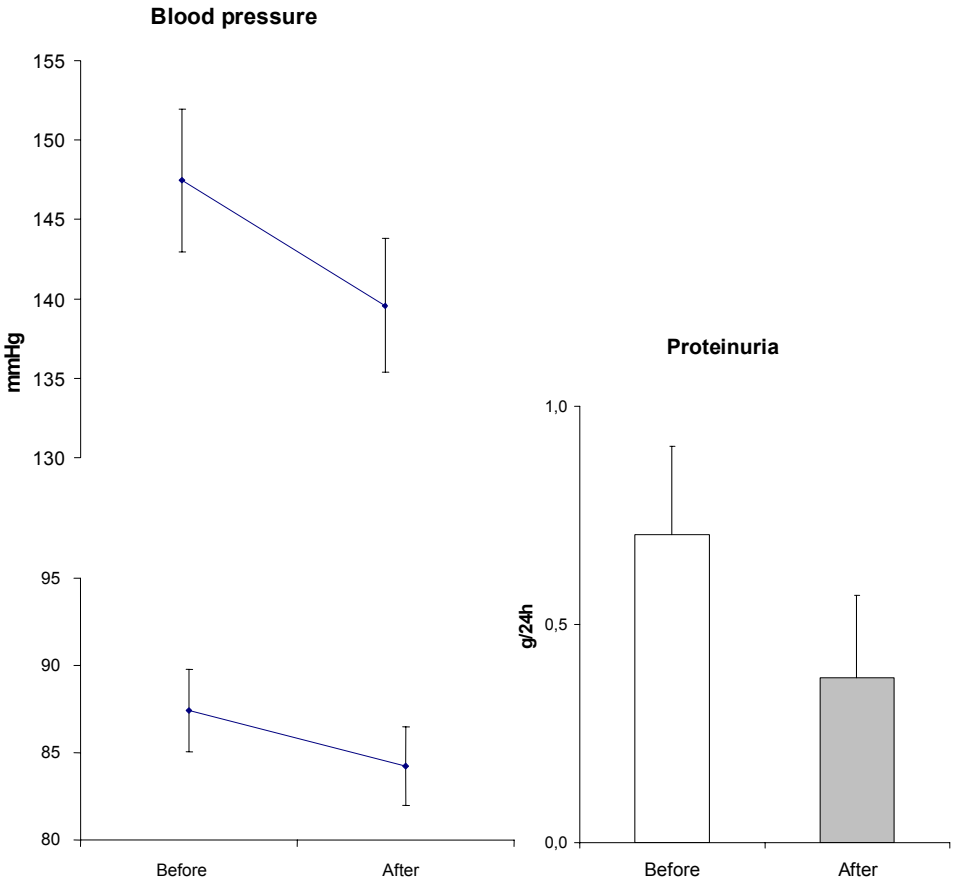

Figure 8. Blood pressure and proteinuria before and after the regular 12-week aerobic water-based exercise.

proteinuria and the degree of glomerulosclerosis in rats compared with sedentary animals but land-based exercise did not improve renal function in small animals (Averbukh, Marcus et al. 1992; Bergamaschi, Boim et al. 1997). Recently it has been shown a beneficial effect of swim training on oxidative stress parameters in rats (Ravi Kiran *et al.* 2004). In the human study performed by Eidemak *et al*. (Eidemak, Haaber et al. 1997), no effect, of land-based exercise (bicycle-ergometric training) on the renal function in patients with moderate renal failure, was found. Decrease of proteinuria in our exercising patients can be observed parallel with the significant lowering of blood pressure (Fig.8). However, also involved are probably the alterations in renal sympathetic activity and levels of plasma angiotensin II in response to the water immersion effect (Epstein 1992). The aquatic environment is an ideal one for mitigation of sympathetic over-activity (Becker and Cole 1998). The decline in sympathetic activity induces a reduction in systemic vascular resistance. An important mechanism is a fall in circulating norepinephrine levels that parallels the reduction in blood pressure (Grossman, Goldstein et al. 1992). One possible contributing factor is increased urinary sodium excretion (Epstein 1992). Furthermore, the renal vasoconstriction can be avoided when exercising in water because in contrary to land-based exercising the renal blood flow increases upon water immersion. Thus, aquatic aerobic exercise seems to be safe concerning the renal function of CRF patients.(III, IV).

It is known that CRF patients have pronounced oxidative stress status (Himmelfarb, Stenvinkel et al. 2002) and in experimental model of CRF the LPO level was high, both in kidney tissue and blood (I).

Mild to moderate exercise has been shown to have protective properties against profound oxidative stress (Arak-Lukmann 2002; Roberts, Vaziri et al. 2002; Edwards *et al.* 2004; Ravi Kiran, Subramanyam et al. 2004). The favourable effect of our exercise conditioning was significant lowering of serum lipid peroxidation in the exercising group (Fig.9). Reduced glutathione higher level in our exercising patients was significantly noticeable after the conditioning program, which shows that anti-oxidative defence was improved after regular exercising. The glutathione redox-ratio normalised and was significantly lower when compared the follow up values to baseline, confirming the anti-oxidative effect of regular exercise (Fig.9).

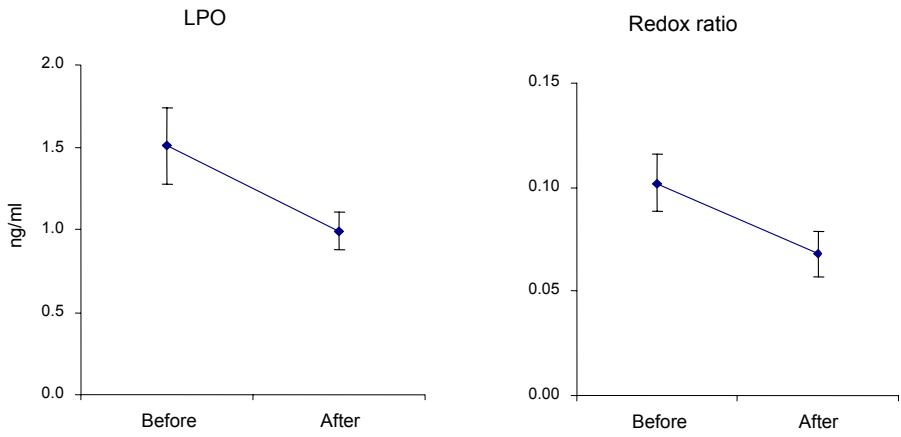

Figure 9. Lipid peroxidation (LPO) and glutathione redox ratio (GSSG/GSH) before and after the regular 12-week aerobic water-based exercise.

All our renal patients received anti-hypertensive medication: ACE-inhibitor alone or in anti-hypertensive combination therapy and their medication was not changed during the rehabilitation programme, so the medication could not have influenced the changes in OxS during the study period.

The anti-hypertensive effect of regular aerobic exercise has been intensively studied, but the factors responsible for the potential lowering of blood pressure are incompletely understood and how exercise diminishes sympathetic tone needs further investigations. Although, the decline in sympathetic activity could induce reduction in systemic vascular resistance, lower arterial blood pressure and ameliorate the systemic OxS status in CRF patients in our study.

The beneficial influences of physical exercise on lipid profile are well known (Ensign *et al.* 2002). Lipid changes in our study also showed an ameliorating tendency (II, IV). The total cholesterol level of the exercise group was improved. In complex rehabilitation practice, dietary advice is an important part, which could reinforce the better outcome of lipid profile but, in our study, participants retained their usual dietary habits. However, to positively improve the plasma lipid profile, dietary means, excess weight reduction and individual motivation to carry on the lifestyle changes should be united (Krook *et al.* 2003).

The results of several studies report of improved psychological well-being and quality of life after exercise (Painter *et al.* 1997; Painter, Carlson et al. 2000). We used a very simple numbered scale for testing the subjective patient-side outcome, which could not be compared with large life quality questionnaires, but there was significant improvement shown in patients' evaluation of their general health status after our aquatic exercise program (IV).

Reduction of proteinuria is the most important goal in progression prevention strategies of chronic nephropathies (Schieppati *et al.* 2003). Thus, the therapies, like aquatic exercise, which can reduce proteinuria and additionally improve subjective well-being and physical functioning should not be overlooked already in the early stages of renal failure to postpone further decline of renal function and prevent a vicious cycle of inactivity, depression and malnutrition with all their patho-physiological consequences.

6. CONCLUSIONS

1. Antihypertensive treatment with renin-angiotensin system blocking agent (losartan) and with a beta-blocking agent (atenolol) lowered blood pressure and diminished proteinuria almost to the same extent in rats with experimental chronic renal failure (remnant kidney).
2. Despite a similar blood pressure lowering efficacy, the progression of aggravated oxidative stress in the kidney tissue, caused by sub-total nefrectomy in rats, was significantly supressed only by the renin-angiotensin system blocking treatment, not by a beta-blocker treatment and the morphological changes in the kidney after 4 weeks of treatment showed less interstitial fibrosis in losartan-treated groups compared with atenolol-treated and untreated animals.
3. The supervised and monitored regular aquatic exercise applied individually for patients with chronic renal disease is a safe and supportive method in complex of renoprotective strategies. It caused significant improvement of renal functional parameters, had beneficial effects on physical capacity and ameliorated significantly the oxidative stress status of chronic renal failure patients.
4. Combination of adequate pharmacological suppression of renin-angiotensin system together with non-pharmacological treatment: regular aquatic exercise, dietary measures, smoking cessation, encouragement and education could preserve renal function, prevent physical worsening and postpone cardiovascular and renal complications in patients with chronic renal disease.

REFERENCES

Abbate, M. and G. Remuzzi (200–243). "Renoprotection: Clues from knockout models of rare diseases." Kidney Int 63(2): 764–6.

Abbate, M, Zoja C, Morigi M, Rottoli D (2002). „ Transforming growth factor-beta 1 is upregulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis." Am J Pathol 161:2179–2199.

Abuja, P. M. and R. Albertini (2001). "Methods for monitoring oxidative stress, lipid peroxidation and oxidation resistance of lipoproteins." Clin Chim Acta 306(1–2): 1–17.

Adler, A. I., R. J. Stevens, S. E. Manley, R. W. Bilous, C. A. Cull and R. R. Holman (2003). "Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64)." Kidney Int 63(1): 225–232.

Agarwal, R. (2003). "Proinflammatory effects of oxidative stress in chronic kidney disease: role of additional angiotensin II blockade." Am J Physiol Renal Physiol 284(4): F863–F869.

Agodoa, L. Y., L. Appel, G. L. Bakris, G. Beck, J. Bourgoignie, J. P. Briggs, J. Charleston, D. Cheek, W. Cleveland, J. G. Douglas, M. Douglas, D. Dowie, M. Faulkner, A. Gabriel, J. Gassman, T. Greene, Y. Hall, L. Hebert, L. Hiremath, K. Jamerson, C. J. Johnson, J. Kopple, J. Kusek, J. Lash, J. Lea, J. B. Lewis, M. Lipkowitz, S. Massry, J. Middleton, E. R. Miller, 3rd, K. Norris, D. O'Connor, A. Ojo, R. A. Phillips, V. Pogue, M. Rahman, O. S. Randall, S. Rostand, G. Schulman, W. Smith, D. Thornley-Brown, C. C. Tisher, R. D. Toto, J. T. Wright, Jr. and S. Xu (2001). "Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial." JAMA 285(21): 2719–28.

Amann, K., A. Koch, J. Hofstetter, M. L. Gross, C. Haas, S. R. Orth, H. Ehmke, L. C. Rump and E. Ritz (2001). "Glomerulosclerosis and progression: effect of subantihypertensive doses of alpha and beta blockers." Kidney Int 60(4): 1309–23.

Amann, K., L. C. Rump, A. Simonaviciene, V. Oberhauser, S. Wessels, S. R. Orth, M. L. Gross, A. Koch, G. W. Bielenberg, J. P. Van Kats, H. Ehmke, G. Mall and E. Ritz (2000). "Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats." J Am Soc Nephrol 11(8): 1469–78.

Amann, K., J. Tornig, B. Kugel, M. L. Gross, K. Tyralla, A. El-Shakmak, A. Szabo and E. Ritz (2003). "Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia." Kidney Int 63(4): 1296–301.

Andersen, S., P. Rossing, T. R. Juhl, J. Deinum and H. H. Parving (2002). "Optimal dose of losartan for renoprotection in diabetic nephropathy." Nephrol Dial Transplant 17(8): 1413–8.

Angeli, F., P. Verdecchia, G. P. Reboldi, R. Gattobigio, M. Bentivoglio, J. A. Staessen and C. Porcellati (2004). "Meta-Analysis of effectiveness or lack thereof of angiotensin-converting enzyme inhibitors for prevention of heart failure in patients with systemic hypertension." Am J Cardiol 93(2): 240–3.

Annuk, M., B. Fellstrom, O. Akerblom, K. Zilmer, T. Vihalemm and M. Zilmer (2001). "Oxidative stress markers in pre-uremic patients." Clin Nephrol 56(4): 308–14.

Annuk, M., M. Zilmer and B. Fellstrom (2003). “Endothelium-dependent vasodilation and oxidative stress in chronic renal failure: Impact on cardiovascular disease.” Kidney Int Suppl(84): 50–3.

Annuk, M., M. Zilmer, L. Lind, T. Linde and B. Fellstrom (2001). “Oxidative stress and endothelial function in chronic renal failure.” J Am Soc Nephrol 12(12): 2747–52.

Aparicio, M., P. Chauveau and C. Combe (2001). “Low protein diets and outcome of renal patients.” J Nephrol 14(6): 433–9.

Arak-Lukmann, A. (2002). “Early rehabilitation of patients with ischaemic heart disease after surgical revascularisation of the myocardium.” Academic dissertation Tartu University Press.

Aros, C. and G. Remuzzi (2002). “The renin-angiotensin system in progression, remission and regression of chronic nephropathies.” J Hypertens 20 Suppl 3: S45–53.

Augustyniak, R. A., M. Tuncel, W. Zhang, R. D. Toto and R. G. Victor (2002). “Sympathetic overactivity as a cause of hypertension in chronic renal failure.” J Hypertens 20(1): 3–9.

Averbukh, Z., E. Marcus, S. Berman, E. Shiloah, T. Horn, J. Weissgarten, A. Golik, M. Cohn, E. Rosenmann and D. Modai (1992). “Effect of exercise training on glomerular filtration rate of mice with various degrees of renal mass reduction.” Am J Nephrol 12(3): 174–8.

Avorn, J., W. C. Winkelmayer, R. L. Bohn, R. Levin, R. J. Glynn, E. Levy and W. Owen, Jr. (2002). “Delayed nephrologist referral and inadequate vascular access in patients with advanced chronic kidney failure.” J Clin Epidemiol 55(7): 711–6.

Baigent, C., K. Burbury and D. Wheeler (2000). “Premature cardiovascular disease in chronic renal failure.” Lancet 356(9224): 147–52.

Bakewell, A. B., R. M. Higgins and M. E. Edmunds (2002). “Quality of life in peritoneal dialysis patients: Decline over time and association with clinical outcomes.” Kidney Int 61(1): 239–48.

Bakris, G. L. and G. A. Mensah (2002). “Pathogenesis and clinical physiology of hypertension.” Cardiol Clin 20(2): 195–206, v.

Bakris, G. L. and J. R. Sowers (2002). “Microalbuminuria in diabetes: focus on cardiovascular and renal risk reduction.” Curr Diab Rep 2(3): 258–62.

Bakris, G. L., M. Williams, L. Dworkin, W. J. Elliott, M. Epstein, R. Toto, K. Tuttle, J. Douglas, W. Hsueh and J. Sowers (2000). “Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group.” Am J Kidney Dis 36(3): 646–61.

Barrett, B. J. (2003). “Applying multiple interventions in chronic kidney disease.” Semin Dial 16(2): 157–64.

Bayorh, M. A., A. A. Ganafa, R. R. Socci, N. Silvestrov and I. K. Abukhalaf (2004). “The role of oxidative stress in salt-induced hypertension.” Am J Hypertens 17(1): 31–6.

Bayorh, M. A., A. A. Ganafa, R. R. Socci, N. Silvestrov, I. K. Abukhalaf and D. Eatman (2004). “The role of oxidative stress in salt-induced hypertension

Effect of losartan on oxidative stress-induced hypertension in Sprague-Dawley rats.” Am J Hypertens 17(1): 31–6.

Becker, B. E. and A. J. Cole (1998). “Aquatic Rehabilitation.” in „Rehabilitation Medicine. Principles and Practice Third Edition.” ed. DeLisa JA, Gans BM (Lippincott-Raven Publishers, Philadelphia): 887–901.

Benigni, A, Corna D, Zoja C, Rottoli D (2002). "Targeted eletion of angiotensin II type 1 receptor does not protect mice from progressive nephropathy of overloaded proteinuria" J Am Soc Nephrol 13:341A

Bergamaschi, C. T., M. A. Boim, L. A. Moura, I. C. Picarro and N. Schor (1997). "Effects of long-term training on the progression of chronic renal failure in rats." Med Sci Sports Exerc 29(2): 169–74.

Beto, J. A. and V. K. Bansal (1998). "Interventions for other risk factors: tobacco use, physical inactivity, menopause, and homocysteine." Am J Kidney Dis 32(5 Suppl 3): S172–83.

Beto, J. A., V. K. Bansal, H. Moore, S. M. Reams, K. Wiesen, K. D. Nolph, R. Khanna, C. Laothong, E. G. Lowrie, R. B. Curtin, N. LePain and D. Schatell (2004). "Medical nutrition therapy in chronic kidney failure: Integrating clinical practice guidelines National Kidney Foundation Council on renal nutrition survey: Past-present clinical practices and future strategic planning. Medical outcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification." J Am Diet Assoc 104(3): 404–9.

Bianchi, S., R. Bigazzi, A. Caiazza and V. M. Campese (2003). "A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease." Am J Kidney Dis 41(3): 565–70.

Binik, Y. M., G. M. Devins, P. E. Barre, R. D. Guttmann, D. J. Hollomby, H. Mandin, L. C. Paul, R. B. Hons and E. D. Burgess (1993). "Live and learn: patient education delays the need to initiate renal replacement therapy in end-stage renal disease." J Nerv Ment Dis 181(6): 371–6.

Blagg, C. R. (1994). "The socioeconomic impact of rehabilitation." Am J Kidney Dis 24(1 Suppl 1): S17–21; discussion S31–2.

Block, G. A., T. E. Hulbert-Shearon, N. W. Levin and F. K. Port (1998). "Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study." Am J Kidney Dis 31(4): 607–17.

Boaz, M., M. Green, M. Fainauru and S. Smetana (2001). "Oxidative stress and cardiovascular disease in hemodialysis." Clin Nephrol 55(2): 93–100.

Boaz, M., S. Smetana, T. Weinstein, Z. Matas, U. Gafter, A. Iaina, A. Knecht, Y. Weissgarten, D. Brunner, M. Fainaru and M. S. Green (2000). "Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial." Lancet 356(9237): 1213–8.

Bolton, C. H., L. G. Downs, J. G. Victory, J. F. Dwight, C. R. Tomson, M. I. Mackness and J. H. Pinkney (2001). "Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and pro-inflammatory cytokines." Nephrol Dial Transplant 16(6): 1189–97.

Boyce, M. L., R. A. Robergs, P. S. Avasthi, C. Roldan, A. Foster, P. Montner, D. Stark and C. Nelson (1997). "Exercise training by individuals with predialysis renal failure: cardiorespiratory endurance, hypertension, and renal function." Am J Kidney Dis 30(2): 180–92.

Brenner, B. M. (1983). "Hemodynamically mediated glomerular injury and the progressive nature of kidney disease." Kidney Int 23(4): 647–55.

Brenner, B. M., M. E. Cooper, D. de Zeeuw, W. F. Keane, W. E. Mitch, H. H. Parving, G. Remuzzi, S. M. Snapinn, Z. Zhang and S. Shahinfar (2001). "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy." N Engl J Med 345(12): 861–9.

Briganti, E. M., R. C. Atkins and S. J. Chadban (2003). "Albuminuria and renal insufficiency prevalence guides population screening." Kidney Int 64(2): 760–1.

Brooks, D. P., B. G. Short, M. J. Cyronak, L. C. Contino, M. DiCristo, Y. X. Wang and R. R. Ruffolo, Jr. (1993). "Comparison between carvedilol and captopril in rats with partial ablation-induced chronic renal failure." Br J Pharmacol 109(2): 581–6.

Brown, M. D., D. R. Dengel, R. V. Hogikyan and M. A. Supiano (2002). "Sympathetic activity and the heterogenous blood pressure response to exercise training in hypertensives." J Appl Physiol 92(4): 1434–42.

Calo, L. A., P. A. Davis, B. Giacon, E. Pagnin, M. Sartori, P. Riegler, A. Antonello, W. Huber and A. Semplicini (2002). "Oxidative stress in kidney transplant patients with calcineurin inhibitor-induced hypertension: effect of ramipril." J Cardiovasc Pharmacol 40(4): 625–31.

Campese, V. M. and E. Krol (2002). "Neurogenic factors in renal hypertension." Curr Hypertens Rep 4(3): 256–60.

Campese, V. M., S. Ye, R. H. Truong and M. Gamburd (2000). "Losartan reduces sympathetic nerve outflow from the brain of rats with chronic renal failure." J Renin Angiotensin Aldosterone Syst 1(2): 202–8.

Ceballos-Picot, I., V. Witko-Sarsat, M. Merad-Boudia, A. T. Nguyen, M. Thevenin, M. C. Jaudon, J. Zingraff, C. Verger, P. Jungers and B. Descamps-Latscha (1996). "Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure." Free Radic Biol Med 21(6): 845–53.

Chade, A. R., M. Rodriguez-Porcel, J. P. Grande, J. D. Krier, A. Lerman, J. C. Romero, C. Napoli and L. O. Lerman (2002). "Distinct renal injury in early atherosclerosis and renovascular disease." Circulation 106(9): 1165–71.

Chuahirun, T., A. Khanna, K. Kimball and D. E. Wesson (2003). "Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes." Am J Kidney Dis 41(1): 13–21.

Clarkson, P., H. E. Montgomery, M. J. Mullen, A. E. Donald, A. J. Powe, T. Bull, M. Jubb, M. World and J. E. Deanfield (1999). "Exercise training enhances endothelial function in young men." J Am Coll Cardiol 33(5): 1379–85.

Clorius, J. H., S. Haufe, A. Schlotmann and U. Haberkorn (2002). "Exercise renography in essential hypertension." Q J Nucl Med 46(4): 311–8.

Clorius, J. H., A. Mandelbaum, T. Hupp, F. Reinbold, I. Zuna, S. Denk, C. Fellhauer and G. van Kaick (1996). "Exercise activates renal dysfunction in hypertension." Am J Hypertens 9(7): 653–61.

Clyne, N., J. Ekholm, T. Jogestrand, L. E. Lins and S. K. Pehrsson (1991). "Effects of exercise training in predialytic uremic patients." Nephron 59(1): 84–9.

Crook, E. D., A. Thallapureddy, S. Migdal, J. M. Flack, E. L. Greene, A. Salahudeen, J. K. Tucker and H. A. Taylor, Jr. (2003). "Lipid abnormalities and renal disease: is dyslipidemia a predictor of progression of renal disease?" Am J Med Sci 325(6): 340–8.

Cruickshank, J. M. (2002). "Renoprotection with antihypertensive agents." Lancet 359(9318): 1693; author reply 1693–4.

Death, C. (1999). "Exercising to fitness on dialysis." Edtna Erca J 25(2): 13–5.

Deicher, R. and W. H. Horl (2003). “Anaemia as a risk factor for the progression of chronic kidney disease.” Curr Opin Nephrol Hypertens 12(2): 139–43.

Deligiannis, A., E. Kouidi, E. Tassoulas, P. Gigis, A. Tourkantonis and A. Coats (1999). “Cardiac effects of exercise rehabilitation in hemodialysis patients.” Int J Cardiol 70(3): 253–66.

DePaul, V., J. Moreland, T. Eager and C. M. Clase (2002). “The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial.” Am J Kidney Dis 40(6): 1219–29.

Diamond, J. R. (1994). “Reactive oxygen species and progressive glomerular disease.” J Lab Clin Med 124(4): 468–9.

DiBona, G. F. (2000). “Nervous kidney. Interaction between renal sympathetic nerves and the renin-angiotensin system in the control of renal function.” Hypertension 36(6): 1083–8.

DiBona, G. F. (2001). “Peripheral and central interactions between the renin-angiotensin system and the renal sympathetic nerves in control of renal function.” Ann N Y Acad Sci 940: 395–406.

DiBona, G. F. (2002). “Sympathetic nervous system and the kidney in hypertension.” Curr Opin Nephrol Hypertens 11(2): 197–200.

Dierkes, J., U. Domrose, A. Ambrosch, J. Schneede, A. B. Guttormsen, K. H. Neumann and C. Luley (1999). “Supplementation with vitamin B12 decreases homocysteine and methylmalonic acid but also serum folate in patients with end-stage renal disease.” Metabolism 48(5): 631–5.

Donmez, G., U. Derici, D. Erbas, T. Arinsoy, A. Onk, S. Sindel and E. Hasanoglu (2002). “The effects of losartan and enalapril therapies on the levels of nitric oxide, malondialdehyde, and glutathione in patients with essential hypertension.” Jpn J Physiol 52(5): 435–40.

Drueke, T. B., T. N. Khoa, Z. A. Massy, V. Witko-Sarsat, B. Lacour and B. Descamps-Latscha (2001). “Role of oxidized low-density lipoprotein in the atherosclerosis of uremia.” Kidney Int Suppl 78: S114–9.

Drueke, T. B. and S. G. Rostand (2002). “Progression of vascular calcification in uraemic patients: can it be stopped?” Nephrol Dial Transplant 17(8): 1365–8.

Edwards, D. G., R. S. Schofield, S. L. Lennon, G. L. Pierce, W. W. Nichols and R. W. Braith (2004). “Effect of exercise training on endothelial function in men with coronary artery disease.” Am J Cardiol 93(5): 617–20.

Eidemak, I., A. B. Haaber, B. Feldt-Rasmussen, I. L. Kanstrup and S. Strandgaard (1997). “Exercise training and the progression of chronic renal failure.” Nephron 75(1): 36–40.

Eknoyan, G., A. S. Levey, N. W. Levin and W. F. Keane (2001). “The national epidemic of chronic kidney disease. What we know and what we can do.” Postgrad Med 110(3): 23–9: quiz 8.

Elian, K. M. and L. J. Hoffer (2002). “Hydroxocobalamin reduces hyperhomocysteinemia in end-stage renal disease.” Metabolism 51(7): 881–6.

Elisaf, M. and D. P. Mikhailidis (2002). “Statins and renal function.” Angiology 53(5): 493–502.

Ensign, W. Y., D. J. McNamara and M. L. Fernandez (2002). “Exercise improves plasma lipid profiles and modifies lipoprotein composition in guinea pigs.” J Nutr Biochem 13(12): 747–753.

Epstein, M. (1992). “Renal effects of head-out water immersion in humans: a 15-year update.” Physiol Rev 72(3): 563–621.
Fatica, R. A. and V. W. Dennis (2002). “Cardiovascular mortality in chronic renal failure: hyperphosphatemia, coronary calcification, and the role of phosphate binders.” Cleve Clin J Med 69(Suppl 3): S21–7.
Fellstrom, B. C., H. Holdaas and A. G. Jardine (2003). “Why do we need a statin trial in hemodialysis patients?” Kidney Int Suppl(84): S204–6.
Ferrario, C. M. (2002). “Use of angiotensin II receptor blockers in animal models of atherosclerosis.” Am J Hypertens 15(1 Pt 2): 9S–13S.
Fitts, S. S., M. R. Guthrie and C. R. Blagg (1999). “Exercise coaching and rehabilitation counseling improve quality of life for predialysis and dialysis patients.” Nephron 82(2): 115–21.
Foley, R. N., P. S. Parfrey and M. J. Sarnak (1998). “Clinical epidemiology of cardiovascular disease in chronic renal disease.” Am J Kidney Dis 32(5 Suppl 3): S112–9.
Forgione, M. A., N. Weiss, S. Heydrick, A. Cap, E. S. Klings, C. Bierl, R. T. Eberhardt, H. W. Farber and J. Loscalzo (2002). “Cellular glutathione peroxidase deficiency and endothelial dysfunction.” Am J Physiol Heart Circ Physiol 282(4): H1255–61.
Fournier, A., C. Presne, R. Makdassi, H. Mazouz and G. Choukroun (2002). “Renoprotection with antihypertensive agents.” Lancet 359(9318): 1694–5.
Fried, L. F., T. J. Orchard and B. L. Kasiske (2001). “Effect of lipid reduction on the progression of renal disease: a meta-analysis.” Kidney Int 59(1): 260–9.
Gajek, J. and D. Zysko (2002). “[The influence of single moderate exercise on the sympathetic nervous system activity in patients with essential hypertension].” Pol Arch Med Wewn 108(6): 1145–50.
Galle, J. (2001). “Oxidative stress in chronic renal failure.” Nephrol Dial Transplant 16(11): 2135–7.
Garg, J. and G. L. Bakris (2002). “Treatment of hypertension in patients with renal disease.” Cardiovasc Drugs Ther 16(6): 503–10.
Goldberg, A. P., E. M. Geltman, J. M. Hagberg, J. R. Gavin, 3rd, J. A. Delmez, R. M. Carney, A. Naumowicz, M. H. Oldfield and H. R. Harter (1983). “Therapeutic benefits of exercise training for hemodialysis patients.” Kidney Int Suppl 16: S303–9.
Golper, T. (2001). “Patient education: can it maximize the success of therapy?” Nephrol Dial Transplant 16 Suppl 7: 20–4.
Gonzales, S., G. O. Noriega, M. L. Tomaro and C. Pena (2002). “Angiotensin-(1–7) stimulates oxidative stress in rat kidney.” Regul Pept 106(1–3): 67–70.
Greco, B. A. and J. A. Breyer (1997). “Cholesterol as a predictor of progression in nondiabetic chronic renal disease.” Contrib Nephrol 120: 48–61.
Griffith, O. W. (1980). “Determination of glutathione and glutathione disulfide using glutathione reductase and 2-vinylpyridine.” Anal Biochem 106(1): 207–12.
Grimm, R. H., Jr., K. H. Svendsen, B. Kasiske, W. F. Keane and M. M. Wahi (1997). “Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial.” Kidney Int Suppl 63: S10–4.
Grossman, E., D. S. Goldstein, A. Hoffman, I. R. Wacks and M. Epstein (1992). “Effects of water immersion on sympathoadrenal and dopa-dopamine systems in humans.” Am J Physiol 262(6 Pt 2): R993–9.

Gurer, H., R. Neal, P. Yang, S. Oztezcan and N. Ercal (1999). “Captopril as an antioxidant in lead-exposed Fischer 344 rats.” Hum Exp Toxicol 18(1): 27–32.
Ha, H. and K. H. Kim (1992). “Amelioration of diabetic microalbuminuria and lipid peroxidation by captopril.” Yonsei Med J 33(3): 217–23.
Halliwell, B. and J. M. C. Gutteridge (1999). “Free Radicals in Biology and Medicine.” Oxford University Press 3rd ed.: 140–163, 393–430.
Hasselwander, O. and I. S. Young (1998). “Oxidative stress in chronic renal failure.” Free Radic Res 29(1): 1–11.
Haugen, E. and K. A. Nath (1999). “The involvement of oxidative stress in the progression of renal injury.” Blood Purif 17(2–3): 58–65.
Haugen, E. N., A. J. Croatt and K. A. Nath (2000). “Angiotensin II induces renal oxidant stress in vivo and heme oxygenase-1 in vivo and in vitro.” Kidney Int 58(1): 144–52.
He, J. and P. K. Whelton (1999). “Elevated systolic blood pressure and risk of cardiovascular and renal disease: overview of evidence from observational epidemiologic studies and randomized controlled trials.” Am Heart J 138(3 Pt 2): 211–9.
Hebert, L. A., T. Greene, A. Levey, M. E. Falkenhain and S. Klahr (2003). “High urine volume and low urine osmolality are risk factors for faster progression of renal disease.” Am J Kidney Dis 41(5): 962–71.
Hebert, L. A., D. N. Spetie and W. F. Keane (2001). “The urgent call of albuminuria/proteinuria. Heeding its significance in early detection of kidney disease.” Postgrad Med 110(4): 79–82, 87–8, 93–6.
Heifets, M., T. A. Davis, E. Tegtmeyer and S. Klahr (1987). “Exercise training ameliorates progressive renal disease in rats with subtotal nephrectomy.” Kidney Int 32(6): 815–20.
Higashi, Y., S. Sasaki, S. Kurisu, A. Yoshimizu, N. Sasaki, H. Matsuura, G. Kajiyama and T. Oshima (1999). “Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide.” Circulation 100(11): 1194–202.
Higashi, Y., S. Sasaki, K. Nakagawa, H. Matsuura, T. Oshima and K. Chayama (2002). “Endothelial function and oxidative stress in renovascular hypertension.” N Engl J Med 346(25): 1954–62.
Himmelfarb, J., P. Stenvinkel, T. A. Ikizler and R. M. Hakim (2002). “The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia.” Kidney Int 62(5): 1524–38.
Holdaas, H., B. Fellstrom, A. G. Jardine, I. Holme, G. Nyberg, P. Fauchald, C. Gronhagen-Riska, S. Madsen, H. H. Neumayer, E. Cole, B. Maes, P. Ambuhl, A. G. Olsson, A. Hartmann, D. O. Solbu and T. R. Pedersen (2003). “Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial.” Lancet 361(9374): 2024–31.
Hooper, L., C. D. Summerbell, J. P. Higgins, R. L. Thompson, N. E. Capps, G. D. Smith, R. A. Riemersma and S. Ebrahim (2001). “Dietary fat intake and prevention of cardiovascular disease: systematic review.” BMJ 322(7289): 757–63.
Horsch, A., E. Ritz, C. C. Heuck, W. Hofmann, E. Kuhne and M. Bisson (1981). “Atherogenesis in experimental uremia.” Atherosclerosis 40(3–4): 279–89.
Hostetter, T. H., J. L. Olson, H. G. Rennke, M. A. Venkatachalam and B. M. Brenner (2001). “Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation.” J Am Soc Nephrol 12(6): 1315–25.

Hostetter, T. H., H. G. Rennke and B. M. Brenner (1982). “Compensatory renal hemodynamic injury: a final common pathway of residual nephron destruction.” Am J Kidney Dis 1(5): 310–4.

Hunsicker, L. G., S. Adler, A. Caggiula, B. K. England, T. Greene, J. W. Kusek, N. L. Rogers and P. E. Teschan (1997). “Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study.” Kidney Int 51(6): 1908–19.

Hyndman, M. E., B. J. Manns, F. F. Snyder, P. J. Bridge, N. W. Scott-Douglas, E. Fung and H. G. Parsons (2003). “Vitamin B12 decreases, but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and possible explanation of hyperhomocysteinemia in end-stage renal disease.” Metabolism 52(2): 168–72.

Ikeda, T., T. Gomi and Y. Sasaki (1994). “Effects of swim training on blood pressure, catecholamines and prostaglandins in spontaneously hypertensive rats.” Jpn Heart J 35(2): 205–11.

Ismail, N., R. Neyra and R. Hakim (1998). “The medical and economical advantages of early referral of chronic renal failure patients to renal specialists.” Nephrol Dial Transplant 13(2): 246–50.

Jacob, F., D. J. Polzin, C. A. Osborne, T. A. Allen, C. A. Kirk, J. D. Neaton, C. Lekcharoensuk and L. L. Swanson (2002). “Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs.” J Am Vet Med Assoc 220(8): 1163–70.

Jacobson, H. R. (1991). “Chronic renal failure: pathophysiology.” Lancet 338(8764): 419–23.

Jang, C., R. J. Bell, V. S. White, P. S. Lee, K. M. Dwyer, P. G. Kerr and S. R. Davis (2001). “Women’s health issues in haemodialysis patients.” Med J Aust 175(6): 298–301.

Johansen, K. L., G. M. Chertow, A. V. Ng, K. Mulligan, S. Carey, P. Y. Schoenfeld and J. A. Kent-Braun (2000). “Physical activity levels in patients on hemodialysis and healthy sedentary controls.” Kidney Int 57(6): 2564–70.

Johansson, M., M. Elam, B. Rundqvist, G. Eisenhofer, H. Herlitz, G. Lambert and P. Friberg (1999). “Increased sympathetic nerve activity in renovascular hypertension.” Circulation 99(19): 2537–42.

Johnston, C. I., J. A. Millar, B. P. McGrath and P. G. Matthews (1979). “Long-term effects of captopril (SQ14 225) on blood-pressure and hormone levels in essential hypertension.” Lancet 2(8141): 493–6.

Kanauchi, M. (2002). “Cigarette smoking affects tubulointerstitial lesions in type 2 diabetes.” Diabetes Care 25(8): 1486–7.

Kaplan, L. N., O. A. Mamer and L. J. Hoffer (2001). “Parenteral vitamin B12 reduces hyperhomocysteinemia in end-stage renal disease.” Clin Invest Med 24(1): 5–11.

Kaplan, N. M. (1998). Clinical Hypertension, Williams and Wilkins.

Kasiske, B. (2003). “Managing dyslipidemias in chronic kidney disease.” Nephrol News Issues 17(5): 81–3, 93.

Kastarinen, MJ, Puska PM, Korhonen MH, Mustonen JN, Salomaa VV, Sundvall JE, Tuomilehto JO, Uusitupa MI, Nissinen AM; LIHEF Study Group (2002). “Non-pharmacological treatment of hypertension in primary health care: a 2-year open randomized controlled trial of lifestule intervension against hypertension in eastern Finland.” J Hypertens 20(12):2505–12.

Kato, S, V. A. Luyckx, M. Ots, K. W. Lee, F. Ziai, J. L. Troy, B. M. Brenner and H. S. MacKenzie (1999). "Renin-angiotensin blockade lowers MCP-1 expression in diabetic rats." Kidney Int 56(3): 1037–48.

Keane, W. F. (2000). "Proteinuria: its clinical importance and role in progressive renal disease." Am J Kidney Dis 35(4 Suppl 1): S97–105.

Keane, W. F. (2001). "Metabolic pathogenesis of cardiorenal disease." Am J Kidney Dis 38(6): 1372–5.

Keane, W. F. and G. Eknoyan (1999). "Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation." Am J Kidney Dis 33(5): 1004–10.

Keane, W. F. and P. A. Lyle (2003). "Recent advances in management of type 2 diabetes and nephropathy: lessons from the RENAAL study." Am J Kidney Dis 41(3 Suppl 2): S22–5.

Kedziora-Kornatowska, K. (1999). "Effect of angiotensin convertase inhibitors and AT1 angiotensin receptor antagonists on the development of oxidative stress in the kidney of diabetic rats." Clin Chim Acta 287(1–2): 19–27.

Kim, S. and H. Iwao (2000). "Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases." Pharmacol Rev 52(1): 11–34.

Kitiyakara, C., J. Gonin, Z. Massy and C. S. Wilcox (2000). "Non-traditional cardiovascular disease risk factors in end-stage renal disease: oxidate stress and hyperhomocysteinemia." Curr Opin Nephrol Hypertens 9(5): 477–87.

Kjeldsen, S. E., B. Dahlof, R. B. Devereux, S. Julius, P. Aurup, J. Edelman, G. Beevers, U. De Faire, F. Fyhrquist, H. Ibsen, K. Kristianson, O. Lederballe-Pedersen, L. H. Lindholm, M. S. Nieminen, P. Omvik, S. Oparil, S. Snapinn and H. Wedel (2002). "Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients With Isolated Systolic Hypertension and Left Ventricular Hypertrophy: A Losartan Intervention For Endpoint Reduction (LIFE) Substudy." JAMA 288(12): 1491–8.

Klag, M. J., P. K. Whelton, B. L. Randall, J. D. Neaton, F. L. Brancati, C. E. Ford, N. B. Shulman and J. Stamler (1996). "Blood pressure and end-stage renal disease in men." N Engl J Med 334(1): 13–8.

Konstantinidou, E., G. Koukouvou, E. Kouidi, A. Deligiannis and A. Tourkantonis (2002). "Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs." J Rehabil Med 34(1): 40–5.

Kouidi, E. (2002). "Exercise training in dialysis patients: why, when, and how?" Artif Organs 26(12): 1009–13.

Krook, A., I. Holm, S. Pettersson and H. Wallberg-Henriksson (2003). "Reduction of risk factors following lifestyle modification programme in subjects with type 2 (non-insulin dependent) diabetes mellitus." Clin Physiol Funct Imaging 23(1): 21–30.

Laaksonen, DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA, Uusitupa MI. (2000) „Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial." Med Sci Sports Exerc 32(9):1541–8.

Lang, C. A., B. J. Mills, H. L. Lang, M. C. Liu, W. M. Usui, J. Richie, Jr., W. Mastropaolo and S. A. Murrell (2002). "High blood glutathione levels accompany excellent physical and mental health in women ages 60 to 103 years." J Lab Clin Med 140(6): 413–7.

Lang, C. A., B. J. Mills, W. Mastropaolo and M. C. Liu (2000). "Blood glutathione decreases in chronic diseases." J Lab Clin Med 135(5): 402–5.

Lea, J. P. and S. B. Nicholas (2002). “Diabetes mellitus and hypertension: key risk factors for kidney disease.” J Natl Med Assoc 94(8 Suppl): 7S–15S.

Lerman, L. O., K. A. Nath, M. Rodriguez-Porcel, J. D. Krier, R. S. Schwartz, C. Napoli and J. C. Romero (2001). “Increased oxidative stress in experimental renovascular hypertension.” Hypertension 37(2 Part 2): 541–6.

Levey, A. S., J. A. Beto, B. E. Coronado, G. Eknoyan, R. N. Foley, B. L. Kasiske, M. J. Klag, L. U. Mailloux, C. L. Manske, K. B. Meyer, P. S. Parfrey, M. A. Pfeffer, N. K. Wenger, P. W. Wilson and J. T. Wright, Jr. (1998). “Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease.” Am J Kidney Dis 32(5): 853–906.

Levey, A. S., J. Coresh, E. Balk, A. T. Kausz, A. Levin, M. W. Steffes, R. J. Hogg, R. D. Perrone, J. Lau and G. Eknoyan (2003). “National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.” Ann Intern Med 139(2): 137–47.

Lewis, E. J. (2003). “Angiotensin II receptor blockade in diabetic nephropathy.” Am J Hypertens 16(1): 100–1.

Lewis, E. J., L. G. Hunsicker, W. R. Clarke, T. Berl, M. A. Pohl, J. B. Lewis, E. Ritz, R. C. Atkins, R. Rohde and I. Raz (2001). “Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.” N Engl J Med 345(12): 851–60.

Lilienthal, K., M. Ilmoja, M. Luman, A. Lõhmus, S. Mesikepp, E. Seppet, K. Kõlvald, A. Auerbach, E. Sinimäe, M. Muliin, L. Piel and M. Ots (2003). “Neeruasendusravi epidemioloogia Eestis.” Eesti Arst(5).

Lim, P. S., N. P. Wang, T. C. Lu, T. H. Wang, W. M. Hsu, E. C. Chan, W. R. Hung, C. C. Yang, I. F. Kuo and Y. H. Wei (2001). “Evidence for alterations in circulating low-molecular-weight antioxidants and increased lipid peroxidation in smokers on hemodialysis.” Nephron 88(2): 127–33.

Llach, F. and F. Velasquez Forero (2001). “Secondary hyperparathyroidism in chronic renal failure: pathogenic and clinical aspects.” Am J Kidney Dis 38(5 Suppl 5): S20–33.

Locatelli, F., D. Alberti, G. Graziani, G. Buccianti, B. Redaelli and A. Giangrande (1991). “Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group.” Lancet 337(8753): 1299–304.

Locatelli, F., B. Canaud, K. U. Eckardt, P. Stenvinkel, C. Wanner and C. Zoccali (2003). “Oxidative stress in end-stage renal disease: an emerging threat to patient outcome.” Nephrol Dial Transplant 18(7): 1272–80.

Locatelli, F., J. B. Cannata-Andia, T. B. Drueke, W. H. Horl, D. Fouque, O. Heimburger and E. Ritz (2002). “Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia.” Nephrol Dial Transplant 17(5): 723–31.

Locatelli, F., M. D’Amico, H. Cernevskis, B. Dainys, M. Miglinas, M. Luman, M. Ots and E. Ritz (2001). “The epidemiology of end-stage renal disease in the Baltic countries: an evolving picture.” Nephrol Dial Transplant 16(7): 1338–42.

Locatelli, F., D. Fouque, O. Heimburger, T. B. Drueke, J. B. Cannata-Andia, W. H. Horl and E. Ritz (2002). “Nutritional status in dialysis patients: a European consensus.” Nephrol Dial Transplant 17(4): 563–72.

Luft, F. C. (2000). “Renal disease as a risk factor for cardiovascular disease.” Basic Res Cardiol 95(Suppl 1): I72–6.
Luft, F. C. (2002). “Angiotensin II, the AT2 receptor, and nuclear factor-kappaB activation.” Kidney Int 61(6): 2272–3.
Luft, F. C. (2002). “Proinflammatory effects of angiotensin II and endothelin: targets for progression of cardiovascular and renal diseases.” Curr Opin Nephrol Hypertens 11(1): 59–66.
Lusis, A. J. (2000). “Atherosclerosis.” Nature 407(6801): 233–41.
Ma, L. J. and A. B. Fogo (2001). “Angiotensin as inducer of plasminogen activator inhibitor-1 and fibrosis.” Contrib Nephrol(135): 161–70.
Mailloux, L. U. (2001). “Hypertension in chronic renal failure and ESRD: prevalence, pathophysiology, and outcomes.” Semin Nephrol 21(2): 146–56.
Mailloux, L. U. and W. E. Haley (1998). “Hypertension in the ESRD patient: pathophysiology, therapy, outcomes, and future directions.” Am J Kidney Dis 32(5): 705–19.
Maiorca, R., G. Brunori, B. F. Viola, R. Zubani, G. Cancarini, G. Parrinello and A. De Carli (2000). “Diet or dialysis in the elderly? The DODE study: a prospective randomized multicenter trial.” J Nephrol 13(4): 267–70.
Maisonneuve, P., L. Agodoa, R. Gellert, J. H. Stewart, G. Buccianti, A. B. Lowenfels, R. A. Wolfe, E. Jones, A. P. Disney, D. Briggs, M. McCredie and P. Boyle (2000). “Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study.” Am J Kidney Dis 35(1): 157–65.
Marcantoni, C., T. H. Jafar, L. Oldrizzi, A. S. Levey and G. Maschio (2000). “The role of systemic hypertension in the progression of nondiabetic renal disease.” Kidney Int Suppl 75: S44–8.
Marlowe, E. (2001). “Rehabilitation concerns in the treatment of patients with chronic renal failure.” Am J Phys Med Rehabil 80(10): 762–4.
Marra, G., P. Cotroneo, D. Pitocco, A. Manto, M. A. Di Leo, V. Ruotolo, S. Caputo, B. Giardina, G. Ghirlanda and S. A. Santini (2002). “Early increase of oxidative stress and reduced antioxidant defenses in patients with uncomplicated type 1 diabetes: a case for gender difference.” Diabetes Care 25(2): 370–5.
Maschio, G., D. Alberti, G. Janin, F. Locatelli, J. F. Mann, M. Motolese, C. Ponticelli, E. Ritz and P. Zucchelli (1996). “Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group.” N Engl J Med 334(15): 939–45.
Massy, Z. A. and T. Nguyen-Khoa (2002). “Oxidative stress and chronic renal failure: markers and management.” J Nephrol 15(4): 336–41.
Mathur, S., S. Devaraj and I. Jialal (2002). “Accelerated atherosclerosis, dyslipidemia, and oxidative stress in end-stage renal disease.” Curr Opin Nephrol Hypertens 11(2): 141–147.
McKenney, J. M. (2003). “Potential Nontraditional Applications of Statins.” Ann Pharmacother 37(7): 1063–1071.
Mezzano, S. A., M. Ruiz-Ortega and J. Egido (2001). “Angiotensin II and renal fibrosis.” Hypertension 38(3 Pt 2): 635–8.

Meyer, K. B. and A. S. Levey (1998). “Controlling the epidemic of cardiovascular disease in chronic renal disease: report from the National Kidney Foundation Task Force on cardiovascular disease.” J Am Soc Nephrol 9(12 Suppl): S31–42.

Mimic-Oka, J., T. Simic, L. Djukanovic, Z. Reljic and Z. Davicevic (1999). “Alteration in plasma antioxidant capacity in various degrees of chronic renal failure.” Clin Nephrol 51(4): 233–41.

Moeller, S., S. Gioberge and G. Brown (2002). “ESRD patients in 2001: global overview of patients, treatment modalities and development trends.” Nephrol Dial Transplant 17(12): 2071–6.

Morrow, J. D. (2000). “The isoprostanes: their quantification as an index of oxidant stress status in vivo.” Drug Metab Rev 32(3–4): 377–85.

Muda, P., P. Kampus, M. Zilmer, K. Zilmer, C. Kairane, T. Ristimae, K. Fischer and R. Teesalu (2003). “Homocysteine and red blood cell glutathione as indices for middle-aged untreated essential hypertension patients.” J Hypertens 21(12): 2329–33.

Muirhead, N. (2001). “The rationale for early management of chronic renal insufficiency.” Nephrol Dial Transplant 16(Suppl 7): 51–6.

Mustonen, J, Syrjanen J, Rantala I, Pasternack A (2001). „ Clinical course and treatment of IgA nephropathy.” J Nephrol 14(6):440–6.

Myllymäki, J, Saha H, Mustonen J, Helin H, Pasternack A (2003). „IgM nephropathy: clinical picture and long-term prognosis.” Am J Kidney Dis 41(2):343–50.

Nakamura, T., K. Saionji, Y. Hiejima, H. Hirayama, K. Tago, H. Takano, M. Tajiri, K. Hayashi, M. Kawabata, M. Funamizu, Y. Makita and A. Hata (2002). “Methylenetetrahydrofolate reductase genotype, vitamin B12, and folate influence plasma homocysteine in hemodialysis patients.” Am J Kidney Dis 39(5): 1032–9.

Nath, K. A., A. J. Croatt and T. H. Hostetter (1990). “Oxygen consumption and oxidant stress in surviving nephrons.” Am J Physiol 258(5 Pt 2): F1354–62.

Nemeth, I., H. Orvos and D. Boda (2001). “Blood glutathione redox status in gestational hypertension.” Free Radic Biol Med 30(7): 715–21.

Oberley, E. T., J. H. Sadler and P. S. Alt (2000). “Renal rehabilitation: obstacles, progress, and prospects for the future.” Am J Kidney Dis 35(4 Suppl 1): S141–7.

O’Byrne, D., S. Devaraj, K. N. Islam, R. Collazo, L. McDonald, S. Grundy and I. Jialal (2001). “Low-density lipoprotein (LDL)-induced monocyte-endothelial cell adhesion, soluble cell adhesion molecules, and autoantibodies to oxidized-LDL in chronic renal failure patients on dialysis therapy.” Metabolism 50(2): 207–15.

Odama, U. and G. Bakris (2000). “Target Organ Damage in Hypertension.” J Clin Hypertens (Greenwich) 2(5): 312–318.

Odoni, G., H. Ogata, C. Viedt, K. Amann, E. Ritz and S. R. Orth (2002). “Cigarette smoke condensate aggravates renal injury in the renal ablation model.” Kidney Int 61(6): 2090–8.

O’Donnell, C. J., P. M. Ridker, R. J. Glynn, K. Berger, U. Ajani, J. E. Manson and C. H. Hennekens (1997). “Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians.” Circulation 95(5): 1132–7.

Onozato, M. L., A. Tojo, A. Goto, T. Fujita and C. S. Wilcox (2002). “Oxidative stress and nitric oxide synthase in rat diabetic nephropathy: Effects of ACEI and ARB.” Kidney Int 61(1): 186–94.

Orth, S. R. (2002). “Smoking and the kidney.” J Am Soc Nephrol 13(6): 1663–72.

Orth, S. R., K. Amann, K. Strojek and E. Ritz (2001). “Sympathetic overactivity and arterial hypertension in renal failure.” Nephrol Dial Transplant 16(Suppl 1): 67–9.
Orth, S. R. and E. Ritz (2002). “The renal risks of smoking: an update.” Curr Opin Nephrol Hypertens 11(5): 483–8.
Orth, S. R., A. Stockmann, C. Conradt, E. Ritz, M. Ferro, W. Kreusser, G. Piccoli, M. Rambausek, D. Roccatello, K. Schafer, H. G. Sieberth, C. Wanner, B. Watschinger and P. Zucchelli (1998). “Smoking as a risk factor for end-stage renal failure in men with primary renal disease.” Kidney Int 54(3): 926–31.
Osato, S., K. Onoyama, S. Okuda, T. Sanai, K. Hori and M. Fujishima (1990). “Effect of swimming exercise on the progress of renal dysfunction in rat with focal glomerulosclerosis.” Nephron 55(3): 306–11.
Ots, M., H. S. Mackenzie, J. L. Troy, H. G. Rennke and B. M. Brenner (1998). “Effects of combination therapy with enalapril and losartan on the rate of progression of renal injury in rats with 5/6 renal mass ablation.” J Am Soc Nephrol 9(2): 224–30.
Ots, M., U. Pechter and A. Tamm (2000). “Characteristics of progressive renal disease.” Clin Chim Acta 297(1–2): 29–41.
Painter, P. (1994). “The importance of exercise training in rehabilitation of patients with end-stage renal disease.” Am J Kidney Dis 24(1 Suppl 1): S2–9; discussion S31–2.
Painter, P., L. Carlson, S. Carey, S. M. Paul and J. Myll (2000). “Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients.” Am J Kidney Dis 35(3): 482–92.
Painter, P., G. Moore, L. Carlson, S. Paul, J. Myll, W. Phillips and W. Haskell (2002). “Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life.” Am J Kidney Dis 39(2): 257–65.
Painter, P., A. L. Stewart and S. Carey (1999). “Physical functioning: definitions, measurement, and expectations.” Adv Ren Replace Ther 6(2): 110–23.
Painter, P. L., L. Hector, K. Ray, L. Lynes, S. Dibble, S. M. Paul, S. L. Tomlanovich and N. L. Ascher (2002). “A randomized trial of exercise training after renal transplantation.” Transplantation 74(1): 42–8.
Painter, P. L., M. J. Luetkemeier, G. E. Moore, S. L. Dibble, G. A. Green, J. O. Myll and L. L. Carlson (1997). “Health-related fitness and quality of life in organ transplant recipients.” Transplantation 64(12): 1795–800.
Palmer, B. F. and R. J. Alpern (2003). “Treating dyslipidemia to slow the progression of chronic renal failure.” Am J Med 114(5): 411–2.
Palmer, C. R., M. J. Brown, G. Mancia and L. M. Ruilope (2003). “Long-term cardiovascular consequences of diuretics vs calcium channel blockers vs angiotensin-converting enzyme inhibitors.” JAMA 289(16): 2066–7; author reply 2069–70.
Paueksakon, P., M. P. Revelo, L. J. Ma, C. Marcantoni and A. B. Fogo (2002). “Microangiopathic injury and augmented PAI-1 in human diabetic nephropathy.” Kidney Int 61(6): 2142–8.
Pedrini, M. T., A. S. Levey, J. Lau, T. C. Chalmers and P. H. Wang (1996). “The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis.” Ann Intern Med 124(7): 627–32.
Pepine, C. J. and E. M. Handberg (2001). “The vascular biology of hypertension and atherosclerosis and intervention with calcium antagonists and angiotensin-converting enzyme inhibitors.” Clin Cardiol 24(11 Suppl): V1–5.

Peterson, J. C., S. Adler, J. M. Burkart, T. Greene, L. A. Hebert, L. G. Hunsicker, A. J. King, S. Klahr, S. G. Massry and J. L. Seifter (1995). "Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study." Ann Intern Med 123(10): 754–62.

Petrella, R. J. (1998). "How effective is exercise training for the treatment of hypertension?" Clin J Sport Med 8(3): 224–31.

Pihl, E., K. Zilmer, T. Kullisaar, C. Kairane, A. Pulges and M. Zilmer (2003). "High-sensitive C-reactive protein level and oxidative stress-related status in former athletes in relation to traditional cardiovascular risk factors." Atherosclerosis 171(2): 321–6.

Pisoni, R., R. Faraone, P. Ruggenent and G. Remuzzi (2002). "Inhibitors of the renin-angiotensin system reduce the rate of GFR decline and end-stage renal disease in patients with severe renal insufficiency." J Nephrol 15(4): 428–30.

Praga, M. and E. Morales (2002). "Renal damage associated with proteinuria." Kidney Int Suppl(82): 42–6.

Prichard, S. (2003). "Risk factors for coronary artery disease in patients with renal failure." Am J Med Sci 325(4): 209–13.

Pueyo, M. E., W. Gonzalez, A. Nicoletti, F. Savoie, J. F. Arnal and J. B. Michel (2000). "Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-kappaB activation induced by intracellular oxidative stress." Arterioscler Thromb Vasc Biol 20(3): 645–51.

Rabbia, F., G. Martini, G. Cat Genova, A. Milan, L. Chiandussi and F. Veglio (2001). "Antihypertensive drugs and sympathetic nervous system." Clin Exp Hypertens 23(1–2): 101–11.

Ravi Kiran, T., M. V. Subramanyam and S. Asha Devi (2004). "Swim exercise training and adaptations in the antioxidant defense system of myocardium of old rats: relationship to swim intensity and duration." Comp Biochem Physiol B Biochem Mol Biol 137(2): 187–96.

Remuzzi, G., P. Ruggenenti and A. Benigni (1997). "Understanding the nature of renal disease progression." Kidney Int 51(1): 2–15.

Rettig, R. (1993). "The kidney as a determinant of hypertension." Nephrol Dial Transplant 8(12): 1317–8.

Rettig, R. and A. Uber (1995). "Hypertension and the kidney: new insights from results of renal transplantation studies." Nephrol Dial Transplant 10 Suppl 9: 9–16.

Ridao, N., J. Luno, S. Garcia de Vinuesa, F. Gomez, A. Tejedor and F. Valderrabano (2001). "Prevalence of hypertension in renal disease." Nephrol Dial Transplant 16(Suppl 1): 70–3.

Ritz, E., K. Amann and D. Fliser (1998). "The sympathetic nervous system and the kidney: its importance in renal diseases." Blood Press Suppl(3): 14–9.

Ritz, E., R. Dikow and L. M. Ruilope (2002). "Renal dysfunction as a cardiovascular risk factor." Curr Hypertens Rep 4(5): 365–8.

Ritz, E., I. Rychlik, F. Locatelli and S. Halimi (1999). "End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions." Am J Kidney Dis 34(5): 795–808.

Ritz, E. and D. C. Tarng (2001). "Renal disease in type 2 diabetes." Nephrol Dial Transplant 16 Suppl 5: 11–8.

Roberts, C. K., N. D. Vaziri and R. J. Barnard (2002). "Effect of diet and exercise intervention on blood pressure, insulin, oxidative stress, and nitric oxide availability." Circulation 106(20): 2530–2.

Rodriguez-Perez, J. C., A. Losada, A. Anabitarte, J. Cabrera, J. Llobet, L. Palop and C. Plaza (1997). "Effects of the novel multiple-action agent carvedilol on severe nephrosclerosis in renal ablated rats." J Pharmacol Exp Ther 283(1): 336–44.

Ross, R. (1999). "Atherosclerosis--an inflammatory disease." N Engl J Med 340(2): 115–26.

Ross, S. D., K. Fahrbach, D. Frame, R. Scheye, J. E. Connelly and J. Glaspy (2003). "The effect of anemia treatment on selected health-related quality-of-life domains: a systematic review." Clin Ther 25(6): 1786–805.

Ruggenenti, P., A. Perna, L. Mosconi, R. Pisoni and G. Remuzzi (1998). "Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN)." Kidney Int 53(5): 1209–16.

Ruggenenti, P., A. Schieppati and G. Remuzzi (2001). "Progression, remission, regression of chronic renal diseases." Lancet 357(9268): 1601–8.

Ruilope, L. M. (1997). "Renoprotection and renin-angiotensin system blockade in diabetes mellitus." Am J Hypertens 10(12 Pt 2): 325S–331S.

Ruilope, L. M. (2002). "The kidney as a sensor of cardiovascular risk in essential hypertension." J Am Soc Nephrol 13(Suppl 3): S165–8.

Ruilope, L. M. (2004). "New European guidelines for management of hypertension: what is relevant for the nephrologist." Nephrol Dial Transplant 19(3): 524–8.

Rump, L. C., K. Amann, S. Orth and E. Ritz (2000). "Sympathetic overactivity in renal disease: a window to understand progression and cardiovascular complications of uraemia?" Nephrol Dial Transplant 15(11): 1735–8.

Rump, L. C., V. Oberhauser and E. Schwertfeger (1999). "Interaction of the autonomic nervous and the renin-angiotensin system in heart and kidney." Nephrol Dial Transplant 14(Suppl 4): 38–9.

Ruoti, R. G., J. T. Troup and R. A. Berger (1994). "The effects of nonswimming water exercises on older adults." J Orthop Sports Phys Ther 19(3): 140–5.

Rutkowski, B., M. Szolkiewicz, J. Korczynska, E. Sucajtys, E. Stelmanska, T. Nieweglowski and J. Swierczynski (2003). "The role of lipogenesis in the development of uremic hyperlipidemia." Am J Kidney Dis 41(3 Suppl 2): S84–8.

Sahadevan, M. and B. L. Kasiske (2002). "Hyperlipidemia in kidney disease: causes and consequences." Curr Opin Nephrol Hypertens 11(3): 323–9.

Sarnak, M. J., B. E. Coronado, T. Greene, S. R. Wang, J. W. Kusek, G. J. Beck and A. S. Levey (2002). "Cardiovascular disease risk factors in chronic renal insufficiency." Clin Nephrol 57(5): 327–35.

Sarnak, M. J. and A. S. Levey (2000). "Cardiovascular disease and chronic renal disease: a new paradigm." Am J Kidney Dis 35(4 Suppl 1): S117–31.

Schieppati, A., G. Remuzzi and N. Perico (2003). "The June 2003 Barry M. Brenner Comgan lecture. The future of renoprotection: frustration and promises Preventing end-stage renal disease: the potential impact of screening and intervention in developing countries." Kidney Int 64(6): 1947–55.

Schiffl, H., S. M. Lang and R. Fischer (2002). "Stopping smoking slows accelerated progression of renal failure in primary renal disease." J Nephrol 15(3): 270–4.

Schmitz, A. and M. Vaeth (1988). “Microalbuminuria: a major risk factor in non-insulin-dependent diabetes. A 10-year follow-up study of 503 patients.” Diabet Med 5(2): 126–34.

Schrier, R. W., J. I. Shapiro, L. Chan and D. C. Harris (1994). “Increased nephron oxygen consumption: potential role in progression of chronic renal disease.” Am J Kidney Dis 23(2): 176–82.

Seghrouchni, I., J. Drai, E. Bannier, J. Riviere, P. Calmard, I. Garcia, J. Orgiazzi and A. Revol (2002). “Oxidative stress parameters in type I, type II and insulin-treated type 2 diabetes mellitus; insulin treatment efficiency.” Clin Chim Acta 321(1–2): 89–96.

Selvaraj, N., Z. Bobby, A. K. Das, R. Ramesh and B. C. Koner (2002). “An evaluation of level of oxidative stress and protein glycation in nondiabetic undialyzed chronic renal failure patients.” Clin Chim Acta 324(1–2): 45–50.

Shephard, R. J. and G. J. Balady (1999). “Exercise as cardiovascular therapy.” Circulation 99(7): 963–72.

Shin, G. T., S. J. Kim, K. A. Ma, H. S. Kim and D. Kim (2000). “ACE inhibitors attenuate expression of renal transforming growth factor-beta1 in humans.” Am J Kidney Dis 36(5): 894–902.

Shlipak, M. G., J. A. Simon, D. Grady, F. Lin, N. K. Wenger and C. D. Furberg (2001). “Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease.” J Am Coll Cardiol 38(3): 705–11.

Shoji, T., E. Ishimura, M. Inaba, T. Tabata and Y. Nishizawa (2001). “Atherogenic lipoproteins in end-stage renal disease.” Am J Kidney Dis 38(4 Suppl 1): S30–3.

Shou, I., L. N. Wang, S. Suzuki, M. Fukui and Y. Tomino (1997). “Effects of antihypertensive drugs on antioxidant enzyme activities and renal function in stroke-prone spontaneously hypertensive rats.” Am J Med Sci 314(6): 377–84.

Siems, W., S. Quast, F. Carluccio, I. Wiswedel, D. Hirsch, W. Augustin, H. Hampi, M. Riehle and O. Sommerburg (2002). “Oxidative stress in chronic renal failure as a cardiovascular risk factor.” Clin Nephrol 58(Suppl 1): S12–9.

Sietsema, K. E., W. R. Hiatt, A. Esler, S. Adler, A. Amato and E. P. Brass (2002). “Clinical and demographic predictors of exercise capacity in end-stage renal disease.” Am J Kidney Dis 39(1): 76–85.

Smith, J. K., R. Dykes, J. E. Douglas, G. Krishnaswamy and S. Berk (1999). “Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease.” JAMA 281(18): 1722–7.

Starkopf, J., K. Tamme, M. Zilmer, R. Talvik and J. Samarutel (1997). “The evidence of oxidative stress in cardiac surgery and septic patients: a comparative study.” Clin Chim Acta 262(1–2): 77–88.

Steiner, R, Wegman I (1925) „Die Rolle des Eiweises im Menschenkörper und die Albuminurie” in „Grundlegendes für eine Erweiterung der Heilkunst” Verlag des Klinisch-Therapeutischen Institutes, Arlesheim, Schweiz: 54–8.

Stenvinkel, P. (2003). “Interactions between inflammation, oxidative stress, and endothelial dysfunction in end-stage renal disease.” J Ren Nutr 13(2): 144–8.

Stenvinkel, P., O. Heimburger, F. Paultre, U. Diczfalusy, T. Wang, L. Berglund and T. Jogestrand (1999). “Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure.” Kidney Int 55(5): 1899–911.

Strawn, W. B. and C. M. Ferrario (2002). “Mechanisms linking angiotensin II and atherogenesis.” Curr Opin Lipidol 13(5): 505–12.

Suematsu, M., H. Suzuki, F. A. Delano and G. W. Schmid-Schonbein (2002). "The inflammatory aspect of the microcirculation in hypertension: oxidative stress, leukocytes/endothelial interaction, apoptosis." Microcirculation 9(4): 259–76.

Suh, M. R., H. H. Jung, S. B. Kim, J. S. Park and W. S. Yang (2002). "Effects of regular exercise on anxiety, depression, and quality of life in maintenance hemodialysis patients." Ren Fail 24(3): 337–45.

Suliman, M. E., P. Stenvinkel, P. Barany, O. Heimburger, B. Anderstam and B. Lindholm (2003). "Hyperhomocysteinemia and its relationship to cardiovascular disease in ESRD: Influence of hypoalbuminemia, malnutrition, inflammation, and diabetes mellitus." Am J Kidney Dis 41(3 Suppl 1): S89–95.

Sun, Y., J. Zhang, L. Lu, S. S. Chen, M. T. Quinn and K. T. Weber (2002). "Aldosterone-induced inflammation in the rat heart : role of oxidative stress." Am J Pathol 161(5): 1773–81.

Sun, Y., J. Zhang, J. Q. Zhang and F. J. Ramires (2000). "Local angiotensin II and transforming growth factor-beta1 in renal fibrosis of rats." Hypertension 35(5): 1078–84.

Sunder-Plassmann, G., M. Fodinger, H. Buchmayer, M. Papagiannopoulos, J. Wojcik, J. Kletzmayr, B. Enzenberger, O. Janata, W. C. Winkelmayer, G. Paul, M. Auinger, U. Barnas and W. H. Horl (2000). "Effect of high dose folic acid therapy on hyperhomocysteinemia in hemodialysis patients: results of the Vienna multicenter study." J Am Soc Nephrol 11(6): 1106–16.

Svarstad, E., O. Myking, J. Ofstad and B. M. Iversen (2002). "Effect of light exercise on renal hemodynamics in patients with hypertension and chronic renal disease." Scand J Urol Nephrol 36(6): 464–72.

Zarazaga, A., L. Garcia-De-Lorenzo, P. P. Garcia-Luna, P. Garcia-Peris, J. Lopez-Martinez, V. Lorenzo, L. Quecedo and J. Del Llano (2001). "Nutritional support in chronic renal failure: systematic review." Clin Nutr 20(4): 291–9.

Zoccali, C., F. Mallamaci, G. Tripepi, F. A. Benedetto, S. Cutrupi, S. Parlongo, L. S. Malatino, G. Bonanno, G. Seminara, F. Rapisarda, P. Fatuzzo, M. Buemi, G. Nicocia, S. Tanaka, N. Ouchi, S. Kihara, T. Funahashi and Y. Matsuzawa (2002). "Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease." J Am Soc Nephrol 13(1): 134–41.

Taal, M. W. and B. M. Brenner (2001). "Evolving strategies for renoprotection: non-diabetic chronic renal disease." Curr Opin Nephrol Hypertens 10(4): 523–31.

Taddei, S., A. Virdis, L. Ghiadoni, I. Sudano and A. Salvetti (2001). "Endothelial dysfunction in hypertension." J Cardiovasc Pharmacol 38(Suppl 2): S11–4.

Tanaka, H., D. R. Bassett, Jr., E. T. Howley, D. L. Thompson, M. Ashraf and F. L. Rawson (1997). "Swimming training lowers the resting blood pressure in individuals with hypertension." J Hypertens 15(6): 651–7.

Tesar, V., T. Zima, M. Jirsa, J. Crkovska, S. Stipek, Z. Vernerova and M. Serakova (2002). "Influence of losartan and enalapril on urinary excretion of 8-isoprostane in experimental nephrotic syndrome." Med Sci Monit 8(2): BR23–8.

Tinucci, T., S. B. Abrahao, J. L. Santello and D. Mion, Jr. (2001). "Mild chronic renal insufficiency induces sympathetic overactivity." J Hum Hypertens 15(6): 401–6.

Tonelli, M., L. Moye, F. M. Sacks, T. Cole and G. C. Curhan (2003). "Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease." J Am Soc Nephrol 14(6): 1605–13.

Tonelli, M., L. Moye, F. M. Sacks, B. Kiberd and G. Curhan (2003). "Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency." Ann Intern Med 138(2): 98–104.

Tozawa, M., K. Iseki, C. Iseki, S. Oshiro, Y. Ikemiya and S. Takishita (2002). "Influence of smoking and obesity on the development of proteinuria." Kidney Int 62(3): 956–62.

Touyz, R. M. (2000). "Oxidative stress and vascular damage in hypertension." Curr Hypertens Rep 2(1): 98–105.

Tran, Z. V. and A. Weltman (1985). "Differential effects of exercise on serum lipid and lipoprotein levels seen with changes in body weight. A meta-analysis." JAMA 254(7): 919–24.

Tremblay, R., A. Bonnardeaux, D. Geadah, L. Busque, M. Lebrun, D. Ouimet and M. Leblanc (2000). "Hyperhomocysteinemia in hemodialysis patients: effects of 12-month supplementation with hydrosoluble vitamins." Kidney Int 58(2): 851–8.

Trevisan, M., R. Browne, M. Ram, P. Muti, J. Freudenheim, A. M. Carosella and D. Armstrong (2001). "Correlates of markers of oxidative status in the general population." Am J Epidemiol 154(4): 348–56.

Tuncel, M., R. Augustyniak, W. Zhang, R. D. Toto and R. G. Victor (2002). "Sympathetic nervous system function in renal hypertension." Curr Hypertens Rep 4(3): 229–36.

Turi, S., A. Friedman, C. Bereczki, F. Papp, J. Kovacs, E. Karg and I. Nemeth (2003). "Oxidative stress in juvenile essential hypertension." J Hypertens 21(1): 145–52.

Turini, G. A., H. R. Brunner, M. Gribic, B. Waeber and H. Gavras (1979). "Improvement of chronic congestive heart-failure by oral captopril." Lancet 1(8128): 1213–5.

Usberti, M., G. M. Gerardi, R. M. Gazzotti, S. Benedini, S. Archetti, L. Sugherini, M. Valentini, P. Tira, G. Bufano, A. Albertini and D. Di Lorenzo (2002). "Oxidative stress and cardiovascular disease in dialyzed patients." Nephron 91(1): 25–33.

Usta, M., A. Ersoy, K. Dilek, B. Ozdemir, M. Yavuz, M. Gullulu and M. Yurtkuran (2003). "Efficacy of losartan in patients with primary focal segmental glomerulosclerosis resistant to immunosuppressive treatment." J Intern Med 253(3): 329–34.

Van Den Akker, J. M., H. B. SJ, A. D. SH, H. V. T. LJ, H. S. AF and R. Van Leusen (2003). "Atorvastatin and simvastatin in patients on hemodialysis: Effects on lipoproteins, C-reactive protein and in vivo oxidized LDL." J Nephrol 16(2): 238–44.

Van den Branden, C., M. Gabriels, J. Vamecq, K. Vanden Houte and D. Verbeelen (1997). "Carvedilol protects against glomerulosclerosis in rat remnant kidney without general changes in antioxidant enzyme status. A comparative study of two beta-blocking drugs, carvedilol and propanolol." Nephron 77(3): 319–24.

van Kats, J. P., M. A. Schalekamp, P. D. Verdouw, D. J. Duncker and A. H. Danser (2001). "Intrarenal angiotensin II: interstitial and cellular levels and site of production." Kidney Int 60(6): 2311–7.

van Kats, J. P., J. R. van Meegen, P. D. Verdouw, D. J. Duncker, M. A. Schalekamp and A. H. Danser (2001). "Subcellular localization of angiotensin II in kidney and adrenal." J Hypertens 19(3 Pt 2): 583–9.

Van Tits, L., J. De Graaf, H. Hak-Lemmers, S. Bredie, P. Demacker, P. Holvoet and A. Stalenhoef (2003). "Increased levels of low-density lipoprotein oxidation in

patients with familial hypercholesterolemia and in end-stage renal disease patients on hemodialysis." Lab Invest 83(1): 13–21.
Wang, N. P., P. S. Lim, T. T. Chen, L. M. Thien, T. H. Wang and W. M. Hsu (2002). "Smoking is associated with alterations of blood thiol-group related antioxidants in patients on hemodialysis." Nephron 92(4): 772–9.
Wirta, O, Pasternack A, Mustonen J, Laippala P (1997). „Renal and cardiovascular predictord of 9-year total and sudden cardiac mortality in non-insulin-dependent diabetic subjects." Nephrol Dial Transplant 12(12):2612–7.
Vanholder, R., R. De Smet, G. Glorieux, A. Argiles, U. Baurmeister, P. Brunet, W. Clark, G. Cohen, P. P. De Deyn, R. Deppisch, B. Descamps-Latscha, T. Henle, A. Jorres, H. D. Lemke, Z. A. Massy, J. Passlick-Deetjen, M. Rodriguez, B. Stegmayr, P. Stenvinkel, C. Tetta, C. Wanner and W. Zidek (2003). "Review on uremic toxins: classification, concentration, and interindividual variability." Kidney Int 63(5): 1934–43.
Vaziri, N. D., M. Dicus, N. D. Ho, L. Boroujerdi-Rad and R. K. Sindhu (2003). "Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency." Kidney Int 63(1): 179–85.
Vaziri, N. D., Z. Ni, F. Oveisi, K. Liang and R. Pandian (2002). "Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in renal insufficiency." Hypertension 39(1): 135–41.
Waugh, N. R. and A. M. Robertson (2000). "Protein restriction for diabetic renal disease." Cochrane Database Syst Rev(2): CD002181.
Weber-Witt, H. (1994). Erlebnis Wasser: Therapeutische Übungen, Springer Verlag.
Weiss, D., D. Sorescu and W. R. Taylor (2001). "Angiotensin II and atherosclerosis." Am J Cardiol 87(8A): 25C–32C.
Welch, W. J. and C. S. Wilcox (2001). "AT1 receptor antagonist combats oxidative stress and restores nitric oxide signaling in the SHR." Kidney Int 59(4): 1257–63.
Wen, Y., J. C. Skidmore, M. M. Porter-Turner, C. A. Rea, M. A. Khokher and B. M. Singh (2002). "Relationship of glycation, antioxidant status and oxidative stress to vascular endothelial damage in diabetes." Diabetes Obes Metab 4(5): 305–8.
Wenger, N. K. (1998). "Lipid metabolism, physical activity, and postmenopausal hormone therapy." Am J Kidney Dis 32(5 Suppl 3): S80–8.
Verbeelen, D. L., D. De Craemer, P. Peeters, K. Vanden Houte and C. Van den Branden (1998). "Enalapril increases antioxidant enzyme activity in renal cortical tissue of five-sixths-nephrectomized rats." Nephron 80(2): 214–9.
Wiberg, E. M. (2003). "[Well-designed training programs crucial for dialysis patients]." Lakartidningen 100(7): 519–26.
Wilson, S. H., A. R. Chade, A. Feldstein, T. Sawamura, C. Napoli, A. Lerman and L. O. Lerman (2003). "Lipid-lowering-independent effects of simvastatin on the kidney in experimental hypercholesterolaemia." Nephrol Dial Transplant 18(4): 703–9.
Wolf, G. (1998). "Angiotensin II is involved in the progression of renal disease: importance of non-hemodynamic mechanisms." Nephrologie 19(7): 451–6.
Wolf, G., U. Butzmann and U. O. Wenzel (2003). "The renin-angiotensin system and progression of renal disease: from hemodynamics to cell biology." Nephron Physiol 93(1): P3–13.
Wright, J. T., Jr., G. Bakris, T. Greene, L. Y. Agodoa, L. J. Appel, J. Charleston, D. Cheek, J. G. Douglas-Baltimore, J. Gassman, R. Glassock, L. Hebert, K. Jamerson, J. Lewis, R. A. Phillips, R. D. Toto, J. P. Middleton and S. G. Rostand (2002).

"Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial." JAMA 288(19): 2421–31.

Yamashita, T., S. Kawashima, Y. Miwa, M. Ozaki, M. Namiki, T. Hirase, N. Inoue, K. Hirata and M. Yokoyama (2002). "A 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitor reduces hypertensive nephrosclerosis in stroke-prone spontaneously hypertensive rats." J Hypertens 20(12): 2465–73.

Ye, S., H. Zhong, V. Yanamadala and V. M. Campese (2002). "Renal injury caused by intrarenal injection of phenol increases afferent and efferent renal sympathetic nerve activity." Am J Hypertens 15(8): 717–24.

Yu, H. T. (2003). "Progression of chronic renal failure." Arch Intern Med 163(12): 1417–29.

Yu, X. Q., L. L. Wu, X. R. Huang, N. Yang, R. E. Gilbert, M. E. Cooper, R. J. Johnson, K. N. Lai and H. Y. Lan (2000). "Osteopontin expression in progressive renal injury in remnant kidney: role of angiotensin II." Kidney Int 58(4): 1469–80

SUMMARY IN ESTONIAN

KROONILISE NEERUPUUDULIKKUSE JA ARTERIAALSE HÜPERTENSIOONI PROGRESSEERUMISE ENNETAMIS STRATEEGIAID

Eksperimentaalne ja kliiniline uuring

Sissejuhatus

Kõrgvererõhutõbi, diabeetiline nefropaatia, krooniline glomerulopaatia ja krooniline tubulointerstitsiaalne nefriit on lõppstaadiumi kroonilise neerupuudulikkuse (KNP) peamisteks põhjusteks. Põhihaigus viib sekundaarse glomerulaarkahjustuseni, mida iseloomustavad proteinuuria, hüpertensioon, valguainevahetuse lõpp-produktide kontsentratsiooni kõrgenemine veres ja glomerulaarfiltratsiooni langus. KNP progresseerumine on tavaliselt nende haiguste puhul aeglane, aastaid, isegi dekaade vältav, kuid viib neeruasendusravi vältimatuseni.

Patogeneesi mehhanismides on oluline osakaal arteriaalse vererõhu tõusul, hüperfiltratsiooni tekkel, oksüdatiivse stressi ja endoteeli düsfunktsiooni kujunemisel. Reniin-angiotensiinsüsteemi (RAS) blokeerivad ravimid on oma renoprotekteeriva toime tõttu eelisravimiteks KNP korral. Loommudelite kasutamine võimaldab uurida KNP patofüsioloogilisi mehhanisme ja morfoloogisi muutusi ning hinnata KNP progresseerumise ennetamiseks manustatavate antihüpertensiivsete ravimite efektiivsust. Oksüdatiivse stressi näitajate dünaamikat mõõtes võib hinnata nii medikamentoosse kui mittemedikamentoosse ravi sobivust ja edukust ka KNP patsientidel.

Neeruhaigust põhjustanud põhihaiguse ravi ja optimaalne KNP ravi võimaldab korrigeerida ja ennetada ureemiast tingitud metabolismihäireid. Põhihaiguse ja KNP medikamentoosse ravi kõrval pööratakse üha enam tähelepanu progresserumise pidurdamisele ja haigete rehabililtatsioonile. Kuna aterosklekoos on KNP haigete puhul oluline probleem, millega seostatakse enneaegset suremust, siis on KNP varajases staadiumis rakendatud meetmed kõige efektiivsemad ja kõige soodsama kaugperspektiiviga nii haigele kui ühiskonnale.

Kroonilise neeruhaigete taastusravi põhisuundadeks on kardiovaskulaarsete tüsistuste tekke ennetamine ja neeruhaiguse süvenemise vältimine. Medikamentoosse kardio- ja renoprotekteeriva ravi kõrval on neeruhaigetel soovitav järgida dieeti, loobuda suitsetamisest, tegelda sobiva kehalise aktiivsusega.

Mittemedikamentoosse ravi uudse võttena kasutati käesolevas töös aeroobset võimlemist basseinis kehalise võimekuse arendamiseks. Vesi avaldab soodsat mõju organismi funktsionaalsetele protsessidele: tõuseb ringleva vere maht,

paraneb venoosne naas südamesse, tõuseb südame väljutusmaht, samaaegselt alaneb pulsisagedus, väheneb sümpaatilise närvisüsteemi aktiivsus, neeru verevoolutus paraneb. Vesivõimlemise mõju KNP haigete neerufunktsioonile ei ole varem uuritud.

Uurimistöö eesmärgid

1. Uurida kroonilise neerupuudulikkuse loommudelil (*remnant kidney*) antihüpertensiivse ravi toimet patofüsioloogilistele ja morfoloogilistele muutustele neerus ning oksüdatiivse stressi näitajatele veres, uriinis ja neerukoes (I).
2. Uurida 12-nädalat kestva taastusravi programmi — aeroobne ravivõimlemine basseinis — mõju hüpertensiooniga ning kerge ja mõõduka neerupuudulikkusega patsientide kardiorespiratoorsele funktsionaalsele seisundile, neerufunktsiooni näitajatele, vere lipiidele ja oksüdatiivse stressi parameetritele ning osalejate tervisega seotud elukvaliteedile (II, III, IV).

I OSA:
Antihüpertensiivse ravi mõju vererõhule, neerufunktsioonile, oksüdatiivse stressi näitajatele ja neerukoe morfoloogilisele leiule kroonilise neerupuudulikkuse loommudelil (artikkel I)

Eksperimentaalse kroonilise neerupuudulikkuse ja sekundaarse hüpertensiooni loommudelina kasutati 5/6 nefrektoomiat (*remnant kidney*) 55 Wistar rotil. Antihüpertensiivse ravina kasutati ühel rühmal RAS blokeerivat vahendit (losartaan), teisel rühmal beeta-blokaatorit (atenolool), ravimata rühm jäi kontrollrühmaks. Loomadel jälgiti dünaamiliselt vererõhku (mõõdetud roti sabal) ja ööpäevase uriini valgusisaldust. Oksüdatiivse stressi näitajad määrati nelja nädala möödudes katse lõpul arteriaalsest verest, neerukoest ja uriinist. Neerukoes hinnati fokaal- segmentaalse glomeruloskleroosi ja interstitsiaalse fibroosi ulatust.

Antihüpertensiivse ravi toimel alanes vererõhk ja vähenes proteinuuria ravitud loomadel oluliselt võrreldes mitteravitutega. Losartaaniga ravitud rühmas oli lipiidse peroksüdatsiooni näitaja neerukoes usutavalt madalam kui atenololiga ravitud ja ravi mittesaanute rühmas. Ka isoprostaanide tase uriinis oli katse lõpul losartaani-rühmas madalam kui atenolooli-rühmas. Korrelatsioon neerukoe lipiidse preoksüdatsiooni taseme ja arteriaalse vererõhu vahel oli statistiliselt usutav. Süsteemse lipiidse peroksüdatsiooni tase veres mõõdetuna ei olnud statistilise erinevusega ravitud loomade ja ravimata loomade vahel.

Eksperimentaalse neeruhaiguse algstaadiumis nelja nädala jooksul tekkis morfoloogiliselt sedastatav fokaalne glomeruloskleroos ja interstitsiaalne

fibroos. Antihüpertensiivset ravi saanud loomadel oli interstitsiaalset fibroosi neerukoes usutavalt vähem kui ravi mittesaanutel.

II OSA:
Vesivõimlemise mõju kroonilise neeruhaigusega patsiendi vererõhule, oksüdatiivse stressi näitajatele ja neerufunktsioonile (artiklid II, III, IV)

Uuringust võttis osa 26 kerge ja mõõduka neerupuudulikkusega hüpertensiivset patsienti (pt), (13 meest, 13 naist) diagnoosidega: I tüüpi suhrkurdiabeet 3 pt, II tüüpi suhkurdiabeet 3 pt, krooniline glomerulonefriit 15 pt, krooniline püelonefriit 1 pt, essentsiaalne hüpertensioon 4 pt, vanuses 31–72 aastat. 17 patsienti moodustasid liikumisravi rühma (I rühm), 9 patsienti, kes ei osalenud liikumisravis, jäid kontrollrühma (II rühm). Patsientide dieedi ja medikamentoosse ravi muudatusi ei toimunud. Individuaalse aeroobse võimekuse tase määrati kardiorespiratoorsel testimisel. Taastusravi rühm võimles basseinis õlgadeni vees vertikaalselt 12-nädala jooksul 2 korda nädalas 30 minutit. Harjutuste intensiivsus oli igale patsiendile individuaalne — vastavalt 40–50% tema isiklikust maksimaalsest hapnikutarbimisest, pulsisagedust mõõdeti sport-testeriga. Vererõhku mõõdeti pärast 15 minutilist puhkust istudes. Oksüdatiivse stressi parameetrid määrati veres, neerufunktsiooni hindamiseks kasutati proteinuuria, glomerulaarfiltratsiooni, seerumi kreatiniini ja tsüstatiin-C väärtuste mõõtmist. Üldise tervisega seotud heaolu seisundi hindamiseks kasutati enne ja pärast liikumisravi programmi lühikest küsimust “Kuidas hindate oma üldist tervislikku seisundit praegu?” Vastust numbrilise skaalaga 1 kuni 10 tähistati järgmiselt: 8–10 hea, 4–7 keskmine, 1–3 vilets.

Liikumisravi rühmas (rühm I) langes arteriaalne vererõhk usutavalt, aeroobse võimekuse tase mõõdetuna maksimaalse hapniku tarbimise alusel suurenes, teised kardiorespiratoorsed näitajad paranesid oluliselt. Proteinuuria ja tsüstatiin-C väärtus vähenesid usutavalt, glomerulaarfiltratsioon paranes. Kontrollrühmas (rühm II) vastavad näitajad jäid samaks või halvenesid.

Oksüdatiivse stressi markerites oli usutav nihe paremusele — lipiidse peroksüdatsiooni taseme näitaja vähenes I rühmas tunduvalt, ka dieenkonjugaadid alanesid, tõusis nii üldglutatiooni kui ka usutavalt redutseeritud glutatiooni tase, glutatiooni redokssuhe vähenes samuti oluliselt, viidates antioksüdantse taseme paranemisele I rühmas. Isoprostaanide väärtus uriinis ei muutunud usutavuse piires. II rühmas usutavaid nihkeid ei sedastatud. I rühma patsientide subjektiivne hinnang vesivõimlemisprogrammi järgsele tervislikule seisundile oli oluliselt paranenud, jäädes aga endiselt vahemikku “elan keskmiselt”.

Kokkuvõte:

1. Antihüpertensiivse ravi tulemusena vähenes kroonilise neerupuudulikkusega loomadel *(remnant kidney)* statistiliselt usutavalt proteinuuria ja alanes vererõhk võrrelduna ravimata loomadega, erinevust reniin-angiotensiin süsteemi blokeeriva ravi (losartaan-rühm) ja beeta-blokaatori (atenoolol-rühm) kasutamise vahel neljanädalasel perioodil ei olnud (I).
2. Statistiliselt oluline paremus oli reniin-angiotensiin süsteemi blokeerival ravil beeta-blokeeriva ravi ees oksüdatiivse stressi näitudele mõõdetuna neerukoes Väiksema raskusastmega morfoloogilisi muutusi neerukoes võis samuti sedastada losartaan-rühmas võrrelduna atenoolool- ja ravimata rühmaga (I).
3. Aeroobne ravivõimlemine basseinis parandas oluliselt neeru funktsionaalset seisundit kroonlise neerupuudulikkusega patsientidel, tõstis kardiorespiratoorset võimekust, alandas usutavalt nii süstoolset kui diastoolset vererõhku ja vähendas oksüdatiivse stressi taset (II, III, IV).
4. Individuaalselt määratud ja piisava regulaarsusega vesivõimlemine evib soodsat mõju kroonilise neeruhaigusega patsientidele ja võib lisaks medikamentoossele neeru kaitsvale reniin-angiotensiin süsteemi blokeerivale ravile olla kasutusel kompleksse taastusravi osana koos dieedisoovituste ja nõustamisega aeglustamaks neerupuudulikkuse progresseerumist (II, III, IV).

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PUBLICATIONS

Ülle Pechter, Marina Aunapuu, Zivile Riispere, Tiiu Vihalemm,
Tiiu Kullissaar, Kersti Zilmer, Mihkel Zilmer, Mai Ots
"Kidney tissue and blood oxidative stress status after losartan and atenolol treatment in experimental renal failure".
Accepted for publication in Nephron Experimental Nephrology, June, 2004

Y. Pechter, J. Maaroos, M. Zilmer, K. Zilmer, S. Mesikepp, A. Veraksits, M. Ots
"The Impact of Aquatic Exercise on Cardio-respiratory, Renal and Lipid Parameters in Chronic Renal Failure Patients" Monduzzi Editore International Proceedings Division ATHEROSCLEROSIS: Risk factors, Diagnosis and Treatment, Salzburg, July 7–10, 2002: 67–70

Ülle Pechter, Jaak Maaroos, Siiri Mesikepp, Alar Veraksits, Mai Ots
"Regular Low-intensity Aquatic Exercise Improves Cardiorespiratory Functional Capacity and Reduces Proteinuria in Chronic Renal Failure Patients"
Nephrology Dialysis. Transplantation, 2003, 18,3: 624–625

Ülle Pechter, Mai Ots, Siiri Mesikepp, Kersti Zilmer, Tiiu Kullissaar,
Tiiu Vihalemm, Mihkel Zilmer and Jaak Maaroos
"Beneficial Effects of Water-based Exercise in the Patients with Chronic Kidney Disease"
International Journal of Rehabilitation Research, 2003, 26(2): 153–156

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1966–1969	Tartu Miina Härma Gymnasium
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Special courses

1994–1995	2-years course of classical natural medicine in Chamber of Physicians of Berlin with 3-month practical assisstance in Berlin Moabit Clinic, department of rehabilitation and natural medicine
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Professional employment

1984–1991	Tartu Childrens Hospital, pediatrician
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Scientific activity

Main research field: Rehabilitation and pathogenesis of hypertension and chronic renal failure; epidemiology of chronic renal failure; life quality and councelling of patients with chronic renal failure. Assessment of oxidative stress and efficacy of antihypertensive medication in animal model of chronic renal failure and hypertension.

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Grants of European Atherosclerosis Society in 2001, 2002.

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Erialane enesetäiendus

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Teaduslik tegevus

Peamised uurimisvaldkonnad: Hüpertensiooni ja kroonilise neeruhaiguse patogenees ja taastusravi, kroonilise neerupuudulikkuse haigete epidemioloogia, elukvaliteet.

Teised uurimisprojektid "Angiotensiin-II retseptor antagonisti toime oksüdatiivsele staatusele omandatud hüpertensiooni eksperimentaalsel mudelil"

Teaduspublikatsioonide üldarv: 37, viis ettekannet rahvusvahelistel konverentsidel.

Saadud uurimistoetused: *European Atherosclerosis Society*, Aastakongresside sõidustipendiumid 2001 ja 2002 aastal.

Teaduslik organisatsiooniline ja erialane tegevus:

Eesti Taastusarstide Selts, liige

Eesti Nefroloogide Selts, liige

Eesti Hüpertensiooni Ühing, liige

Society of European Classical Natural Medicine, liige

International Society of Anthroposophical Physicians, liige

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