

Clinical Manifestations of Chronic Renal Insufficiency

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Introduction

Progression to end-stage renal disease (ESRD) is characterized by the disruption of a number of biological functions, including fluid and electrolyte balance, intermediate metabolism, and endocrine, neurological, hematological, cardiovascular, gastrointestinal, cutaneous and ophthalmologic functions. This brings about a large and characteristic cohort of clinical manifestations that constitute the uremic syndrome. Uremia starts to declare itself to patient and physician when renal function drifts below 30%. However, individual manifestations do not appear simultaneously, but rather depend on the degree of loss of glomerular filtration rate (GFR); on the concomitance or pre-existence of other pathologies such as diabetes mellitus (DM), coronary artery disease (CAD), and peripheral vascular disease (PVD); and on the individual predisposition of a patient. The following review of the clinical manifestations and management of the uremic syndrome is limited to the period preceding the institution of renal replacement therapy (RRT).

Water and Electrolyte Balance

Water Balance

Progressive loss of the structural integrity of the nephrons and anatomical derangement of the renal medulla causes loss of renal responsiveness to anti-diuretic hormone (ADH). This, along with the increased single-nephron GFR and the increased filtered load of solutes such as urea, impairs the renal concentrating and diluting functions. Under these conditions, the urine approaches isosthenuria, i.e. urine osmolality equal to that of serum, and the solute excretion becomes the main determinant of water excretion. The practical consequence of this phenomenon is that patients with advanced renal insufficiency are at risk of developing either dehydration and hypernatremia, or water intoxication and hyponatremia, when water intake is less or more, respectively, than mandated by the solute load.

Sodium (Na⁺) Balance

Na⁺ load per nephron increases as renal function is progressively lost, and both humoral and renal tubule adaptative mechanisms are activated to decrease tubular Na⁺ reabsorption and to maintain Na⁺ balance. In

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advanced renal insufficiency, excessive Na^+ intake tends to cause Na^+ retention and volume overload because of the preexisting maximal or close-to-maximal depression of renal tubule reabsorption. Conversely, the ability to lower Na^+ excretion during Na^+ restriction is hindered by the increased osmotic diuresis per nephron. Thus, patients with advanced renal insufficiency tend to develop volume overload or volume depletion, respectively, when the dietary Na^+ intake is excessively large or small.

Potassium (K^+) Balance

As is the case with Na^+ , the K^+ load per nephron increases in advanced renal failure. Differently from Na^+ , however, K^+ balance is maintained primarily by changes in tubular secretion rate. This is accomplished primarily by activation of the renin-angiotensin system and consequent increased distal tubular K^+ excretion. Large intestine excretion of K^+ is also responsive to this hormonal system, and it contributes some to the maintenance of K^+ homeostasis in chronic renal failure (CRF). The importance of the renin-angiotensin-aldosterone axis in the maintenance of K^+ balance is underscored by the observation that CRF patients with anatomic damage of the juxtaglomerular apparatus and with hyporeninemic hypoaldosteronism frequently experience hyperkalemia. Even when this hormonal system is normally functional, patients with CRF usually do not tolerate excessive dietary K^+ intake or the use of β -adrenergic receptor agonists, nonselective beta blockers (which impair K^+ entry into cells), nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and K^+ -sparing diuretics (which impair tubular K^+ excretion).

Intermediate Metabolism

Protein Metabolism and Calorie Requirement

The minimum daily protein requirement of moderately active healthy adults in energy balance is commonly set at 0.6 g/kg/day of high biological value proteins. In Western postindustrial societies, the average protein intake is higher than 1 g/kg/day and includes a large proportion of high biological value proteins. Healthy individuals tolerate this excess of proteins relatively well due to biochemical pathways that dispose of surplus amino acids. Conversely, patients with advanced renal insufficiency cope poorly with excessive protein intake. Inability to dispose of the degradation products derived from excess protein intake leads to accumulation of: (1) nitrogen moieties that contribute to uremic symptoms, (2) titratable acid leading to metabolic acidosis, (3) phosphates with secondary hyperparathyroidism, and (4) Na^+ with volume expansion and arterial hypertension. An increased renal load of osmotically active moieties and phosphates is also believed to accelerate the progressive loss of renal function. Additionally, recent observations indicate that unrestricted protein intake is harmful for patients with the nephrotic syndrome, as it seems to worsen these individuals' proteinuria and hypoalbuminemia.

For these reasons, protein-restricted diets have been utilized for > 3 decades in the management of patients with CRF [1, 2]. The soundness and safety of this practice has been corroborated over the years by a large body of clinical observations and experimental studies which show:

- protein-restricted diets do indeed prevent or ameliorate many symptoms and com-

plications of CRF and they might slow the progressive loss of renal function;

- the rates of amino acid metabolism and the energy expenditure of nonacidotic patients with CRF are not different from those of healthy controls, both at rest and during exercise [3, 4]; and
- normal subjects and patients with CRF are equally able to achieve neutral nitrogen balance when fed low amounts of high biological value proteins (0.6 g/kg body weight/day), as long as they are provided with adequate amounts of energy (≥ 35 kcal/kg/day) [5].

Despite these findings, most studies of patients on dialysis indicate that these individuals are malnourished [6, 7] and that malnutrition often antedates the dialysis therapy [8]. This is of major concern since malnutrition at the onset of ESRD is a potent predictor of increased morbidity and mortality, as shown in studies with up to 5 years of follow-up [9, 10]. Protein and/or energy intake below the thresholds given above are important contributing factors [11], because it is known that patients with GFR below 25% tend to suffer from anorexia [12]. In addition, it is believed that accelerated protein catabolism may be as important in promoting malnutrition. Conditions that promote protein degradation during advanced renal insufficiency include

- inadequate energy intake in concomitance with a protein-restricted diet, because patients with CRF are unable to adapt to low protein diets when the caloric intake is < 35 kcal/kg/day;
- metabolic acidosis, which starts to develop with a GFR < 40 mL/min [13];
- depressed anabolic effect of insulin on muscle protein synthesis; and
- chronic inflammatory conditions with increased pro-inflammatory cytokine activity.

Treatment

Protein restriction should be implemented in those patients who are motivated and capable of following the rather stringent rules of this diet. The goals of nutritional therapy are to prescribe a diet sufficient to prevent malnutrition, to diminish the accumulation of nitrogenous waste and metabolic disturbances characteristic of uremia, and to slow the progression of renal failure. Protein intake is determined based on the degree of renal insufficiency, the presence of progressive renal failure, the level of proteinuria, the presence of diabetic nephropathy, and the concomitant use of glucocorticoids.

Lipid Metabolism

Abnormal serum lipid and lipoprotein concentrations are present early in patients with CRF and are only marginally affected by the degree of renal failure and by the use of dialysis. This metabolic abnormality is a likely important contributor to the high incidence of atherosclerosis and cardiovascular disease in the CRF population. Although total cholesterol is frequently normal, the serum concentrations of low-density lipoproteins (LDL) and high-density lipoproteins (HDL) cholesterol tend to be high and low, respectively. Triglyceride levels are often elevated, due to low lipoprotein lipase activity and impaired conversion of very-low density lipoproteins (VLDL) to LDL. Low activities of lipoprotein lipase, hepatic triglyceride lipase and lecithin cholesterol acyltransferase result in accumulation of intermediate density lipoproteins (IDL) and reduction of HDL. Factors such as insulin resistance or deficiency, hyperparathyroidism, carnitine deficiency, and altered

lipoprotein content of the VLDLs have been proposed as contributors to the decreased lipase activity. Recently, several groups have reported the frequent occurrence of high levels of lipoprotein(a) (Lp(a)) and of oxidized lipid moieties in the circulation of patients with ESRD [14 – 16] and CRF [17]. The observation that both Lp(a) and oxidized lipids contribute to cardiovascular disease in subjects with normal renal function justifies the recent interest in the possible role of these factors in the progression of atherosclerosis in renal patients. Interestingly, high blood levels of both Lp(a) and oxidized lipids are favored by increased oxidative stress and chronic inflammation, conditions that frequently occur in CRF patients.

Treatment

Because accelerated atherosclerosis and cardiovascular disease are the leading cause of morbidity and mortality in patients with CRF, prophylactic treatment of these conditions should be considered in patients with chronic renal insufficiency. Unfortunately, very limited information is currently available on the effectiveness of long-term lipid reduction therapy in this patient population, and most of the practices in this area are based on clinical trials in populations without renal disease. In general, these patients should be instructed to follow the American Heart Association step 1 diet, which provides < 30% of total calories from fat and < 10% of total calories from saturated fat. Also, all patients are urged to achieve desirable body weight and to maintain cardiovascular fitness with daily exercise. Pharmacological intervention with β -hydroxy- β -methyl glutaryl coenzyme A (HMG-CoA) has been proposed for individuals with LDL persistently > 140 mg/dL

[18]. Gemfibrozil can also be used with pronounced lowering effects on the triglycerides and some modest effect on LDLs [19]. The practice of prescribing antioxidants such as high dose α -tocopherol is gaining popularity to reduce oxidative stress and ameliorate the chronic inflammation seen in these patients. However, high-dose ascorbic acid (vitamin C) should be avoided because of the tendency of this moiety to be converted to oxalic acid, resulting in oxalosis.

Carbohydrate Metabolism

Moderate and advanced renal insufficiency is associated with glucose intolerance, caused in part by acquired resistance of the target organs to the insulin action. In these patients, normal binding of insulin to its receptor is not followed by adequate activation of the postreceptor pathways that mediate this hormone's cellular actions. An additional cause of glucose intolerance in renal insufficiency is the abnormal pancreatic release of insulin in response to glucose. Secondary hyperparathyroidism contributes to the latter abnormality because PTH increases intracellular levels of calcium. These metabolic aberrances may require the institution of exogenous insulin therapy in patients with noninsulin-dependent (Type II) DM who develop moderate renal insufficiency. Paradoxically, the insulin requirement of diabetics with renal insufficiency tends to decrease as the renal function falls below 20%, due to reduced renal degradation of proinsulin, C-peptide, and both endogenous and exogenous insulin, resulting in higher blood levels of these peptides.

Immunity, Inflammation and Oxidative Stress

Both humoral [20, 21] and cellular immunity [22] are compromised as renal function is progressively lost [23]. This acquired immunodeficiency state contributes to increased infection risk [24], anergy, poor response to vaccines, and decreased autoimmune disease activity. Paradoxically, this immunodeficiency state is associated with sustained activation of several cell types that participate in the host defense, including the monocytic cell line [25]. Activated monocytes and macrophages are integral elements of the smoldering multifactorial inflammatory state that is often detected in renal failure patients. This develops early in the course of renal failure and is characterized by the presence of high circulating levels of C-reactive protein (CRP) [26, 27], lipopolysaccharide binding protein [28], interleukins IL-1 β and IL-6, and tumor necrosis factor- α (TNF) [29, 30], as well as the presence of cytokine-specific inhibitors, including interleukin-1 receptor antagonist (IL-1Ra) and tumor necrosis factor soluble receptors (TNFRs) [31]. This chronic inflammatory state is intimately linked to increased monocytic and neutrophilic production of reactive oxygen species. Since both exogenous and endogenous antioxidants such as α -tocopherol [32, 33], ascorbic acid [34], superoxide dismutase [35], and the glutathion system [36] are decreased in CRF, the high production of reactive oxygen species results in oxidative damage and further stimulates inflammation [37 – 39]. Indeed, markers of lipid and protein oxidation are elevated in advanced chronic renal insufficiency [40 – 42]. During the last decade, evidence has accumulated to suggest that inflammation and oxidative stress contribute substantially to the

high morbidity and mortality of renal failure patients by promoting anorexia, wasting, malnutrition [43, 44], accelerated atherosclerosis [45] and premature cardiovascular disease [46].

Treatment

Prospective studies demonstrating the safety, efficacy, and cost effectiveness of measures aimed at identifying and treating inflammation and oxidative stress in the renal failure population are lacking. Based on the currently available evidence, the measurement of CRP seems a reasonable test to survey patients with chronic renal disease for signs of chronic inflammation and oxidative stress. High levels should prompt a search for potentially correctable causes, such as infections, drug allergies, autoimmune disease, and cancer. Also, a therapeutic trial with antioxidants may be considered. Alpha-tocopherol is a good candidate since it is a potent dietary antioxidant, its level is low in renal failure patients, and it does not present any specific toxicity for the renal failure population. Ascorbic acid has a synergistic effect with α -tocopherol in its antioxidant activity. However, prudence should be exercised, since it is converted to oxalic acid and may cause oxalosis.

Endocrine Systems

Divalent Ion, Parathyroid Hormone (PTH) and Vitamin D Metabolism

Early signs of altered mineral homeostasis can be detected in most patients with 50% reduction of GFR, although the laboratory

and clinical signs become obvious in all patients when the GFR is $< 25 - 30\%$. During progressive loss of renal mass, the remaining functional tissue adapts by decreasing tubular reabsorption of ultrafiltered phosphorus (Pi), leading to increased single-nephron excretion of this ion. In advanced renal failure, the fractional excretion (FE) of Pi can be as high as 90% [47, 48]. This compensatory mechanism allows maintenance of adequate renal Pi clearance until the GFR is $< 20 - 25$ mL/min, at which point the residual renal mass is often unable to handle the normal dietary intake of Pi and hyperphosphatemia develops. Serum calcium (Ca) declines progressively in moderate and advanced renal insufficiency, due in part to the formation of Ca-Pi products (see above), but mostly because of progressive development of calcitriol deficiency and of target-organ resistance to this hormone, leading to inadequate intestinal absorption of Ca. The calcitriol deficiency is caused primarily by the progressive loss of renal mass, which is essential for the production of calcitriol, and also by the inhibitory effect of hyperphosphatemia on the renal production of this hormone. Hyperphosphatemia, hypocalcemia and calcitriol deficiency are stimuli to the production of PTH, and they all contribute to the development of secondary hyperparathyroidism. The clinical consequences of these divalent ion and hormonal abnormalities are secondary hyperparathyroidism, renal osteodystrophy, and soft tissue calcifications [49]. Hypocalcemia develops slowly and it becomes symptomatic (muscle twitching or frank tetany) almost exclusively associated with an abrupt rise of systemic pH, which in turn causes a fall in ionized Ca. Soft tissue calcifications usually occur when the Ca-Pi product (both expressed in mg/dL) exceeds 70 and they affect primarily the blood vessels, skin, cornea, and periarticular tissues. Pseudo/gout, i.e. intraarticular deposition of

Ca pyrophosphate crystals, with clinical manifestations indistinguishable from those of gout, can occur in patients with advanced renal insufficiency. High blood levels of PTH and skin deposition of Ca-Pi products are important contributors to the development of pruritus. Prior to the diagnosis of ESRD, renal osteodystrophy is most often asymptomatic, although the most severe cases of secondary hyperparathyroidism are associated with early onset of bone pain and skeletal deformities. Additionally, patients with severe secondary hyperparathyroidism have a high rate of bone turnover with excess release of Pi from bone, which can contribute substantially to the maintenance of hyperphosphatemia.

Treatment

In patients with moderate to severe renal insufficiency, serum Pi should be maintained at 4.0 – 5.5 mg/dL. Reductions of Pi intake to 10 mg/kg/day, which is implemented primarily to slow the progression of the renal failure, contribute to the control of hyperphosphatemia. Small amounts of Pi binders are often required once the GFR is below 25%. Ca acetate and Ca carbonate are the most popular choices [50]; aluminum-containing Pi binders should be avoided even at this stage of renal disease. Organic polymer-based phosphate binders have been tested successfully, and they were recently introduced to the market [51]. Serum Ca levels should be maintained in the normal range. Intake of Ca-containing Pi binders with meals inevitably results in intestinal absorption of small amounts of Ca. Serum Ca levels > 10.0 mg/dL should be avoided to prevent further deterioration of renal function. When serum Ca is low and Pi is normal, Ca salts can be given between meals to increase Ca absorption without interfering with the absorption of dietary Pi. Cir-

culating intact PTH should be checked once yearly to rule out the presence of advanced secondary hyperparathyroidism. If PTH is > 3-fold above the upper limit of normal, therapy with calcitriol should be started at the low dose of 0.125 µg/day. This calcitriol dose is effective at reducing circulating PTH without causing deleterious effects such as hypercalciuria, hypercalcemia or loss of renal function [52, 53]. Hypercalcemia is a rare event in the predialysis population, and it should be avoided to prevent further renal damage.

Reproductive System

Dysfunction of the hypothalamic-pituitary-gonadal axis becomes clinically apparent with a GFR < 20 mL/min. Men and women are affected alike, although the deficiency is more obvious in men. In both genders, sexual desire and activity are inversely proportional to the severity of uremia [54]. Indifference to sexual activity can develop with advanced renal failure. In women, menstrual irregularities consistently follow the deterioration of the renal function. Oligomenorrhea occurs with GFR < 15 ml/min and amenorrhea occurs once the GFR is below 5 ml/min. In men, decreased libido and performance develop as the renal function deteriorates and impotence is present in as many as 56% of men with ESRD [55]. The testicles are soft and atrophic, and spermatogenesis is impaired or absent. Gynecomastia occurs more often after dialysis is started. Adolescents suffer from delayed puberty with retardation of skeletal growth. The pathogenesis of these abnormalities seems to be related to direct or indirect effects of uremia on both the hypothalamic-pituitary system and on the gonads. The roles of anemia, zinc deficiency and secondary hyperparathyroidism have been reported. Relatively fre-

quent issues that come up in young women with renal disease are the counseling and management of pregnancy. Pregnancy outcome is 90% successful in women with a serum creatinine < 1.5 mg/dL [56, 57]. When the serum creatinine is > 1.5 mg/dL, the therapeutic abortion rate is 13 – 24% [58, 59], and 56 – 63% of deliveries are preterm, mostly due to worsening renal function, hypertension, abruptio placentae, and fetal distress [60, 61]. Fetal survival ranges from 60 – 92% with highest frequencies in the most recent reports [62]. The presence of maternal hypertension seems to substantially affect the fetal outcome, since preterm birth and growth retardation are more common in hypertensive than normotensive women [63]. Recent progress in medical and pharmacologic management of mother and fetus may continue to improve the fetal outcome in women with chronic renal insufficiency and hypertension.

Growth Hormone System

Growth hormone and the radioimmunoassayable levels of the insulin-like growth factors (IGFs) are elevated in renal failure. However, the bioassayable levels of the IGFs are low due to the presence in the uremic serum of low-molecular-weight inhibitors of the IGFs. This accounts for the stunted growth of children with renal insufficiency, which responds favorably to exogenous administration of recombinant human growth hormone.

Thyroid Hormone

Total thyroxine (T₄), free thyroxine index (FTI), total triiodothyronine (T₃) and free triiodothyronine index tend to be low in renal

failure while the reverse T3 level is normal. Despite these hormonal abnormalities, the thyroid-stimulating hormone (TSH) and the basal metabolic rate are normal.

Hematology

Hematopoietic System

The hemoglobin concentration in azotemia has roughly the same prognostic significance as the creatinine level [64]. In over 90% of the patients with CRF, the hematocrit (HCT) starts to fall when the creatinine clearance reaches 30 – 35 mL/min. Exceptions are patients with polycystic kidney disease (PKD), acquired multicystic disease, hypertensive nephrosclerosis, and some diabetics who can maintain normal HCTs well into end-stage renal disease (ESRD). The anemia is usually normochromic and normocytic. The most important factor by far in the development of anemia is the decreased production of erythropoietin, which normally regulates the bone marrow erythrocyte production. Other factors include:

- resistance to erythropoietin due to deficiency of iron or folic acid; reticuloendothelial blockade from infections, cancer and inflammatory states [65 – 68]; myelofibrosis; aluminum intoxication [69]; bone marrow fibrosis secondary to severe hyperparathyroidism [70, 71];
- shortened erythrocyte life span [72] and possibly neocytolysis [73]; and
- occult bleeding.

Anemia has a profound effect on these patients' general well being and on the performance of their cardiovascular and central nerv-

ous systems. Anemia results in progressive reduction of activity and energy level and of exercise tolerance [74]. This is associated with left ventricular dilatation and diastolic dysfunction [75]. Additionally, anemia causes deterioration of the cognitive function and contributes to the neurobehavioral syndrome of uremia that is characterized by confusion, inability to concentrate, decreased mental alertness and impaired memory [76, 77]. The association between anemia, intractable pruritus, and high circulating histamine concentration was reported in a subset of CRF patients [78]. Anemia has also been implicated in the impairment of sexual function that is common in patients with CRF [79].

Treatment

The mainstay of anemia management is the systemic administration of recombinant human erythropoietin (rHu-Epo) with concomitant adequate support of iron stores. rHu-Epo is started when the HCT drops below 30%. A starting dose of 100 – 150 U/kg 3 times/week achieves HCTs > 35% within 4 weeks. The dose is subsequently adjusted to approximately 25 U/kg once weekly, based on individual response [80]. Initiation of rHu-Epo therapy must be preceded by assessment of iron stores. Iron should be replaced to maintain the transferrin saturation > 16% and ferritin > 80 µg/L. In resistant cases, occult blood loss, hemolysis, inflammation, infection, malignancy, aluminum toxicity, vitamin B12 and folate deficiency, myelofibrosis, red cell enzyme defect and hemoglobinopathies should be considered and corrected [81]. Nephrectomy of failed allografts, empiric treatment with broad spectrum antibiotics, and a cycle of steroids may be considered [82].

Coagulation System

The bleeding tendency is characterized by prolonged bleeding time, and it is rarely of clinical consequence before the GFR falls below 15%. The pathogenesis relates to dysfunction of platelet aggregability, but also to abnormal function of the vascular endothelial wall, to aberrant interaction of platelets and endothelium and to the anemia. Treatment of the bleeding diathesis is required before surgical procedures and during active bleeding. Correction of concomitant anemia with transfusions or rHu-EPO injections are often effective at shortening the bleeding time. 1-deamino-8-D-arginine (DDAVP), either 0.3 µg/kg intravenously (IV) or 3 mg/kg intranasally, restores hemostasis within 30 – 120 minutes and for as long as 8 hours, although repeated administration quickly results in tachyphylaxis. Transfusions of cryoprecipitate are effective for 12 – 18 hours from the time of infusion, but they carry a risk of transmitting viral infections. Conjugated estrogens (0.6 mg/kg/day for 5 days) correct hemostasis one day after administration and last for up to 2 weeks.

Cardiovascular System

Systemic Hypertension

Hypertension is the initial cause of renal disease in approximately 3% of Caucasians and 16% of African-Americans with CRF [83]. Conversely, hypertension develops in virtually all cases of CRF secondary to glomerular and renal small vessel disease, and in 40 – 70% of the cases secondary to tubulointerstitial disease. Hypertension is one of

the earliest manifestations of chronic renal insufficiency, since it is diagnosed even with minimal loss of renal function and can precede the onset of most signs and symptoms of uremia by many years. Hypertension of renal disease accelerates the progression of the already present renal damage and the development of congestive heart failure (CHF), CAD, and cerebrovascular disease. The major factors involved in the pathogenesis and maintenance of hypertension in CRF are salt and water retention, enhanced activity of the renin-angiotensin system, and increased sympathetic tone. Other possible contributors are the decreased production of the endothelium-relaxing factor nitric oxide and the presence in the circulation of inhibitors of the Na-K-ATPase pump.

Treatment

Treatment of hypertension is essential in CRF, because it slows down the progression of the renal damage and decreases morbidity and mortality. The definition of satisfactory blood pressure control in renal failure is not well established, although the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) recommends controlling the blood pressure to 130/85 mmHg (mean arterial pressure (MAP) 100 mmHg) in individuals without proteinuria and to 125/75 (MAP 92 mmHg) in individuals with > 1 g/day of proteinuria [84]. The management of the hypertension of CRF presents 3 major challenges:

- hypertension is often severe and difficult to control, thus requiring the use of ≥ 2 medications;
- the choice of the antihypertensive agents must take into account the coexistence of several medical conditions that can be

- exacerbated by antihypertensive therapy, including DM, dyslipidemias, LVH, and accelerated atherosclerosis; and
- the pharmacology of many antihypertensive agents is altered in renal failure, often leading to special posology requirements, to altered type and frequency of side effects as compared to the normal renal function population, and in some instances to outright contraindication of their use.

Nonpharmacologic intervention should include restriction of sodium chloride intake to < 6 g/day (100 mmol of elemental Na⁺), daily moderate exercise, and weight reduction. Pharmacologic intervention often starts with a diuretic which, for GFR < 50%, should always be a loop diuretic. For these levels of compromise in renal function, the thiazides should be used only as an adjunct to loop diuretics in the rare cases of resistance to loop diuretics. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers have been shown to have renal protective effects. When tolerated, they can be either added to the diuretic or used as first-line agent. When ACE inhibitors and Ang II receptor blockers are not tolerated, the calcium channel blockers are a good alternative. The nondihydropyridine calcium channel blockers (verapamil and diltiazem) seem to have renal protective effects of somewhat lesser magnitude than the ACE inhibitors, although not all studies have reported this effect. Conversely, the dihydropyridine calcium channel blockers (nifedipine, amlodipine, felodipine, isradipine, and nocardipine) appear to be neutral in terms of renal-protective effects. Beta-blockers are a good alternative to ACE inhibitors, Ang II receptor blockers, and calcium channel blockers. The selection of a beta-blocker should try to match the pharmacologic features of the individual drug

with each patient's special needs. Beta-blockers with intrinsic sympathetic activity (Table 1) can be prescribed in the attempt to minimize unwanted effects on lipid metabolism and exercise tolerance. Beta-blockers with poor lipid solubility can be chosen to minimize diffusion in the nervous system and the occurrence of central nervous system (CNS) side effects. β_1 -selective blockers should be prescribed when the presence of CAD is documented or strongly suspected. Beta-blockers with extensive hepatic elimination can be used when toxicity due to excess accumulation is a concern. Central alpha agonists (clonidine) and peripheral alpha-adrenergic receptor blockers (terazosin and doxazosin) are effective third-choice antihypertensives. Minoxidil and hydralazine are potent peripheral vasodilators that are often effective in cases of tenaciously resistant hypertension.

Cardiac Function

Congestive heart failure (CHF) is often present in patients with advanced renal insufficiency. Ischemic heart disease, hypertrophic and/or dilated cardiomyopathy are frequently present and should be managed with the same diagnostic and therapeutic principles that apply to cardiac patients with normal renal function. Manifestations of CRF that often participate in the development and/or exacerbation of CHF are hypertension, anemia, fluid overload, and electrolyte abnormalities including hyperkalemia, hypocalcemia, and acidosis. These should be carefully looked for and aggressively treated and prevented. Uremia per se is believed to affect myocardial contractility, the most convincing evidence coming from the incidental observation of improved cardiac function after renal transplantation and from animal studies [85]. Disturbances of

Table 1. Pharmacological Properties of Beta-blockers. Modified from [88]

Drug	Trade name	β_1 - Selectivity	Intrinsic Symp. Activity	d Blockade	Lipid Solubility	Renal Elimination	Dose
Acebutolol	Sectral	+	+	-	++	0	200 – 800 qd
Atenolol	Tenormin	++	-	-	-	100	12.5 – 25 qd
Betaxolol	Kerlone	++	0	-	-	0	5 – 20 qd
Bisoprolol	Zebeta	++	0	-	++	50	2.5 – 5 qd
Carteolol	Cartrol	0	+	-	-	100	1.25 – 2.5 qd
Carvedilol	Coreg	-	0	+	++	10	12.5 – 50 bid
Celiprolol	Selectol	++	+	-	-	50	200 – 400 qd
Labetalol	Normodyne	-	+	+	+++	60	200 – 1200 bid
Metoprolol	Lopressor	++	-	-	+++	0	50 – 200 bid
Nadolol	Corgard	-	-	-	-	100	40 – 320 qd
Penbutolol	Levatol	-	+	-	+++	0	10 – 20 qd
Pidolol	Visken	-	+++	-	++	40	10 – 60 qd
Propranolol	Inderal LA	-	-	-	+++	0	40 – 480 qd
Timolol	Blocadern	-	-	-	-	20	20 – 60 bid

qd = daily, bid= twice daily

the cardiac rhythm are relatively frequent in renal insufficiency and are mostly related to electrolyte imbalance (hyperkalemia, hypermagnesemia, hypocalcemia, acidosis) or to drug toxicity (digoxin, procainamide, renally-excreted β -blockers). Pericarditis used to occur in about half of the patients who died from uremia before the advent of dialysis. Currently, this condition is much less frequent and is almost always detected once ESRD is reached. Uremic pericarditis in advanced renal insufficiency is a fibrinous inflammatory process. Onset of pericarditis is in itself an indication for initiation of chronic RRT.

Neurologic System

Peripheral Neuropathy

Peripheral neuropathy develops early in chronic renal insufficiency, and abnormalities of the nerve conduction velocity test are often detected much earlier than the onset of symptoms. The onset of symptoms is insidious but very frequently present once the GFR is < 30 mL/min. Peripheral neuropathy is symmetrical, insidious in onset, and slowly progressive. It begins distally and spreads proximally, with the lower extremities being affected first. It is sensorimotor, with the sensory involvement preceding the motor involvement. It is indistinguishable from diabetic neuropathy

and the 2 very often overlap. Loss of 2-point discrimination, vibratory perception, and paresthesias are common. When the GFR is < 15 mL/min, the restless-leg syndrome can occur, with sensations of crawling, prickling and pruritus that worsen with rest and in the evening and improve with movement. The burning-feet syndrome is less frequent and characterized by tenderness and sensation of swelling of the lower extremities. The motor deficit occurs later and is characterized by loss of deep tendon reflexes, weakness of dorsiflexion of the feet, limb weakness, and unsteady gait. The neurological deficit is only partially reversed by RRT, with Wallerian degeneration and neuron loss accounting for the irreversible component of the syndrome. Presence of severe peripheral neuropathy is an indication for initiation of RRT, since procrastination can result in irreversible damage. Low dose tricyclics (e.g. amitriptyline) are moderately effective. The author has had favorable anecdotal experience prescribing the anticonvulsant gabapentin for treatment of symptoms related to peripheral neuropathy [86, 87].

Autonomic Dysfunction

The most frequent and troublesome manifestation is gastroparesis, which overlaps with diabetic gastroparesis. Other manifestations are orthostatic hypotension, impaired sweating and abnormal response to the Valsalva maneuver.

Uremic Encephalopathy

Patients with GFR < 20 mL/min can develop symptoms of reduced general cerebral activity with disturbances of mentation and

cognition. These symptoms are more frequent and pronounced in the elderly, especially if uremia is superimposed on preexisting organic damage of the brain. Frequent initial symptoms are apathy, fatigue, confusion, narrowed attention span, impaired memory, and somnolence. The normal sleep pattern is often affected with altered day-night rhythm. More advanced symptoms, that usually occur with GFR < 10 mL/min, are disorientation, irritability, inappropriate behavior, hallucinations, delusion, anxiety, lethargy, stupor, and coma. The latter more advanced symptoms are almost never experienced nowadays, because of intervention with RRT.

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