REVIEW

Chronic complications in hemodialysis: correlations with primary renal disease

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Abstract

Although hemodialysis technique has improved in the last decades and the accessibility to this life-sustaining treatment modality increased rapidly, we are still concerned about the morbidity and mortality rates of dialysis patients. While technical advances are increasing the efficacy and safety of renal replacement therapies, latest studies are focused on other outcomes: increasing survival rates and the quality of life by an adequate management of the complications in chronic renal patients. This article reviews the complications of chronic hemodialysed patient with special considerations for the role of the primary renal disease that caused renal failure.

Keywords: chronic kidney disease, hemodialysis, primary renal disease, complications.

Introduction

Although hemodialysis technique has improved in the last decades, morbidity and mortality of chronic hemodialysed patients remained high. The researches conducted up to present allowed a decrease of acute intradialytical complications by improving of ultrafiltration technique, composition of dialysis fluid or by introduction of more biocompatible membranes; the alternative of continuous hemodialysis or hemodiafiltration techniques represented also a progress in maintaining alive the patients with stage 5 chronic kidney disease (CKD) and cardiovascular instability.

Several factors may explain the increased morbidity of chronic hemodialysed patients. Increased accessibility to renal replacement therapies allowed prolonged follow up of some categories of patients considered, in the years immediately following the discovery of the hemodialysis technique, to have contraindication for dialytic therapy because of the associated comorbidities: cancer, diabetes, elderly, etc. Increasing survival of uremic patients by dialysis allowed disclosing specific complications of this period. Abundant researches allow the introduction of new therapies with beneficial effects for specific complications of dialytic period, but with notable side effects as well: hypertension or other cardiovascular complications induced by treatment with erythropoiesis stimulating agents, cardiovascular calcifications favored by calcium-containing binders or by vitamin D_3 analogues, etc. Although it is proven a common pathway for CKD progression, the primary renal disease influences not only the progression toward the end stage of renal disease (ESRD), but the patients' evolution after initiating dialysis therapy as well, by the magnitude of residual renal function or through specific complications/comorbidities.

Complications of chronic hemodialysed patients can be classified into two categories:

- specific complications of ESRD with their modifications by hemodialysis therapy;
- complications of the primary renal disease which lead to chronic renal failure.

Evolution of uremia-specific complications after initiating hemodialysis

Cardiovascular complications

Cardiovascular disease represents the major cause of death in chronic dialyzed patients [1]. Hemodialysis removal of excessive salt and water allows the control of systemic blood pressure in more than 80% of patients (with volume-dependent hypertension); it also removes various uremic toxins involved in pathogenesis of hypertension. On the other hand, initiation of hemodialysis increases the incidence and severity of cardiovascular complications by several specific factors [1–4]:

- a voluminous arteriovenous fistula can precipitate or exacerbate congestive heart failure;
- secondary hyperparathyroidism, calcium-containing binders or vitamin D analogues can induce vascular and cardiac calcifications [5];
- erythropoiesis stimulating agents can exacerbate previous hypertension [6];
- hyperhomocysteinemia;
- inadequate intradialysis ultrafiltration;
- rapid electrolyte changes during dialysis session;
- hyperlipidemia and accelerated atherosclerosis of uremic patients;
- dialysis pericarditis, endocarditis.

Gastrointestinal disorders

Fetor and uremic peritonitis disappear after initiating hemodialysis, but other gastrointestinal complications may occur [9, 17]:

- reduced dose of dialysis may lead to anorexia, nausea;

▪ the increased risk of gastritis and gastrointestinal bleeding is maintained due to heparin administration during the hemodialysis sessions or drugs that stimulate gastric acid secretion; severe secondary hyperparathyroidism and hypercalcemia may also increase gastric acid secretion [5];

▪ colonic diverticulosis is noted in long-term dialyzed patients, especially those with polycystic kidneys [7];

▪ ascites may occur due to chronic volemic overload; sometimes it accompanies polycystic liver disease;

▪ increased frequency of angiodysplasia;

▪ hemosiderosis due to excessive transfusions and martial therapy was observed especially during pre-erythropoietin period [7];

▪ iron therapy and calcium-containing binders may cause constipation; other phosphate binders may have laxative effects;

▪ prolonged therapy with antibiotic may lead to pseudo-membranous colitis [7].

Anemia

Anemia does not improve after initiating hemodialysis; additional factors occur [2, 3]:

▪ chronic hemolysis: direct traumatic effect produced by the dialysis circuit on the red blood cells; toxic substances in the dialysate (accidentally – copper, chloramine, nitrates, zinc, fluorine, etc.); prolonged reduced doses of dialysis; abnormal changes of temperature/ osmolarity of dialysis solution;

▪ iron deficiency by: reduced intestinal absorption of iron from the diet; digestive, genital or urinary hemorrhages; blood loss in dialysor and dialysis circuit; repeated venous puncture for routine laboratory tests;

▪ folates deficiency may occur following poor diet intake or due to loss through the dialysis membrane;

▪ repeated transfusions inhibit synthesis and secretion of endogenous erythropoietin;

▪ aluminum intoxication after abuse of aluminum-based phosphate binders or excessive increase of aluminum concentration in dialysate;

▪ secondary severe hyperparathyroidism can produce marrow fibrosis with decreased erythropoiesis rate [5].

Therapy with erythropoiesis stimulating agents may be accompanied by several complications: onset of hypertension or worsening of previous hypertension [1], thrombosis of the vascular access, erythrocytosis, aplastic anemia [6].

Bleeding diathesis of uremia

Initiating hemodialysis improves bleeding time by removal of uremic toxins responsible for platelets dysfunction and secondary to anemia correction, but the bleeding tendency of chronic hemodialysed patients is maintained because of new factors [2, 3]:

▪ contact of blood with the dialysis membrane activates platelets or monocytes with cytokines release and secretion of large amounts of nitric oxide from endothelium;

▪ use of heparin during dialysis sessions is accompanied by an increase of bleeding time and may induce thrombocytopenia;

▪ antiplatelet drugs in vascular patients.

Chronic hemodialysed patients with HIV-associated nephropathy may have gastrointestinal bleeding secondary to Kaposi's sarcoma, non-Hodgkin's lymphoma or colitis with cytomegalovirus [2]. Spontaneous retroperitoneal bleeding may occur in uremic patients with periarteritis nodosa [8]. Intracerebral hematoma occurs especially in patients treated with oral anti-coagulants or those with severe hypertension [1, 2].

Pulmonary complications

Pulmonary infections are very common in uremic patients due to their depressed immunity [7]. In long-term hemodialysed patients, pleural effusion can be noted, sometimes hemorrhagic because of heparin use during hemodialysis sessions. As in the case of dialysis-associated pericarditis or ascites, the etiopathogenesis seems to be chronic inadequate dialysis dose; other causes of pleural effusion – viral or bacterial infections, systemic disease, congestive heart failure, severe hypoproteinemia, etc. – must be excluded before a diagnosis of dialysis-associated pleurisy is established [8].

Bone disorders

Native vitamin D deficiency and secondary hyperparathyroidism are noted early in the course of CKD. Initiating hemodialysis does not influence the evolution of these complications that continue to worsen in the absence of therapy.

Treatment for secondary hyperparathyroidism is often accompanied by several side effects, especially cardiovascular [5]:

▪ hypercalcemia and increased calcium-phosphorus product, with vascular and coronary calcifications have been documented after excessive calcium-containing phosphate binders and/or vitamin D therapy;

▪ adynamic bone disease may be a result of excessive vitamin D_3 therapy.

Hemodialysis can amplify bone disease in CKD.

Aluminum intoxication – from a contaminated dialysate, aluminum-based phosphate binders or secondary to sodium citrate therapy for metabolic acidosis – may be responsible for low turnover bone diseases; aluminum bone toxicity is associated with severe neurologic and hematologic complications: hypochromic microcytic anemia due to erythropoiesis suppression, encephalopathy, cachexia [2].

Non-aluminum osteomalacia is noted in states with negative calcium balance (reduced dietary intake, low calcium concentration in dialysis solution), or in patients with chronic tubulointerstitial nephropathy which have long-standing metabolic acidosis [2]. Adynamic bone diseases are present especially in patients with diabetic nephropathy or in those with granulomatous diseases (tuberculosis, sarcoidosis, etc.) that are accompanied by vitamin D hypersecretion and hypercalcemia [5, 9].

Patients who have been on dialysis for at least 5–7 years can develop dialysis amyloidosis, secondary to osteoarticular depositions of β_2-microglobulin; these protein deposits stimulate osteoclastic resorption of the bone [2, 5].

Neurologic manifestations

Uremic encephalopathy and neuropathy are remitted after initiating hemodialysis. Instead, other specific complications may occur [2]:

▪ complications secondary to primary renal disease – hypertensive encephalopathy in patients with hypertension, peripheral neuropathy in vasculitis, myopathy in systemic diseases (diabetes, lupus, amyloidosis) [8, 9];

▪ complications of hemodialysis therapy:

– dialysis dementia;

– subdural hematoma;

– Wernicke acute encephalopathy (thiamine deficiency);

– encephalopathy secondary to biotin deficiency;

– mononeuropathy – median nerve: carpal tunnel syndrome due to local storage of β_2-microglobulin, median nerve compression by a voluminous arteriovenous fistula or the steal syndrome with secondary nerve ischemia;

▪ iatrogenic complications: aminoglycoside or erythromycin therapy can result in acoustic-vestibular nerve damage and cause permanent deafness; drugs-associated myositis (clofibrate, colchicine, prednisone);

▪ several inter- or intradialytic electrolyte disturbances may induce muscle cramps (hyponatremia), seizures (hyponatremia) or myositis (hypophosphatemia).

Carbohydrate metabolism

Glucose intolerance and peripheral resistance to insulin – specific to the final stage CKD – are reversed after removal of uremic toxins by dialysis. Although hemodialysis normalizes the half-life of insulin, increased risk of hypoglycemia is maintained in chronic dialyzed patients with severe secondary hyperparathyroidism or malnutrition [2]. Initiation of hemodialysis in an insulin-dependent diabetic patient brings unpredictable changes in insulin requirements: on one hand the peripheral resistance to insulin is restored, so the need for insulin would decrease, on the other hand dialysis normalizes the half-life of insulin, therefore the insulin need increases [2, 9].

Protein malnutrition

Uremia is a hypercatabolic state; factors involved are: low protein intake, increased plasma hypercatabolic hormones that are insufficiently degraded by the kidney (glucagon, cortisone, catecholamine), tissue resistance to anabolic hormone actions as a result of accumulation of uremic toxins [7]. Hemodialysis largely corrects these problems by removal of the toxins, normalizing the half-life of catabolic hormones and also by allowing a normal or hyperproteic diet. It brings, however, various disadvantages [2]: hemodialysis itself is a catabolic maneuver by releasing of proteases from erythrocytes or by amino acid loss during the dialysis session. During dialysis with glucose-free solutions, sudden decrease of blood glucose and insulin may occur, leading to periodic hormone stimulation of protein catabolism.

The risk of protein malnutrition persists and is more pronounced even after initiation of dialysis in patients with chronic glomerulopathies and nephrotic syndrome with heavy proteinuria or in patients with malabsorption of various causes (diabetic neuropathy, congestive heart failure, liver cirrhosis, etc.) [2, 9].

Plasma creatinine decrease in a chronic hemodialysed patient is a marker for malnutrition, not for efficient dialysis, and it is a negative prognostic factor. It is associated with hypoalbuminemia, decreased protein synthesis and reduced muscle mass [2].

Lipid metabolism

CKD is characterized by type IV of hyperlipoproteinemia with increased VLDL and IDL and decreased HDL, with the late subclass β-VLDL emerge [7], due to: decreased activity of hepatic lipase and lipoprotein-lipase caused by the accumulation of toxins with inhibittory effect, hyperinsulinism, secondary hyperparathyroidism, excessive dietary fats. Severe dyslipidemia explains accelerated atherosclerosis in uremic patients [2, 7]. After initiating dialytic therapy, dyslipidemia does not correct and may even aggravate; although the lipoprotein-lipase inhibitors are removed from the uremic serum, at the site of blood–dialysis membrane HDL are lost. Serum triglycerides levels are high; heparin is, probably, implicated in this process. Dyslipidemia is more pronounced in patients with nephrotic syndrome and in those with diabetic nephropathy [2, 9].

Cutaneous manifestations

Stage 4 CKD is characterized by various cutaneous complications; the majority persists or increases after initiating dialysis:

▪ pruritus persists in most patients; secondary hyperparathyroidism is the main etiological factor, but increased levels of serum serotonin and histamine may participate [2];

▪ xerosis is secondary to perspiratory glands dysfunction, hypervitaminosis A, hyperparathyroidism [2];

▪ characteristic sallow pallor due to anemia and retentions of urochromes and carotenoid pigments; in some patients a brown diffuse hyperpigmentation can occur due to melanotropic hormone blood accumulation which is poorly dialyzed [2];

▪ cutaneous calcifications – secondary to hyperparathyroidism [5];

▪ hemodialysis-associated bullous dermatitis is associated with normal serum porphyrin levels and is due to an allergic reaction to some chemical substances in the dialysis tubing set; sometimes, drugs are involved (furosemide, tetracycline, nalidixic acid) [2].

Gonadal function

Gonadal function shows partial improvement after initiating dialysis [2]. In men, some improvements in sexual function are noted, especially in the context of erythropoietin therapy [2], but without increasing the serum testosterone. Women menstruation may reappear and prolactinemic levels are normalized, but cycles are usually anovulatoric, most of hemodialysed patients being infertile. Chronic dialysed women rarely become pregnant and carry the pregnancy to term; spontaneous

abortions, death of the fetus *in utero* or at birth, premature births and preeclampsia are frequently noted.

Vitamins

Due to dietary restrictions and loss from the dialysis membrane, hydrosoluble vitamin supplements are required in patients requiring dialysis [2]. Liposoluble vitamins – with the exception of vitamin D – do not require supplementation outside dietary intake.

Immunological abnormalities

CKD is characterized by a progressive decrease of immunity and hemodialysis may enhance immune deficiency. Infections occur frequently in hemodialysed patients, being the second cause of mortality in this group.

The cellular immune response, as well as humoral response is depressed [7].

Proliferation of T-lymphocytes is defective in uremic stage due to accumulation of uremic toxins and excessive transfusions. Erythropoietin therapy partially improves cellular immune response [7]. In hemodialysed patients there is evidence of activation of T-lymphocytes due to blood interaction with the dialysis membrane: the number of antigen presenting cells and the concentration of IL-2 are increased, which worsen the inflammatory state of the patients, the tendency for malnutrition and increased risk of infections.

In chronic hemodialysed patients, humoral immune response may be altered in a characteristic fashion [2]. Although immunoglobulin serum values are normal, normal antibody reactions are depressed. Meanwhile, due to blood contact with dialysis membrane, autoantibodies and anti-ethylenoxid antibodies occur with increased frequency.

Accessory immunity cells are dysfunctional in chronic hemodialysed patients. During the hemodialysis session, blood contact with membranes made of materials with reduced biocompatibility leads to monocyte activation with proinflammatory cytokine release (IL-1β, TNF-α, IL-6). At the beginning of the hemodialysis session neutrophilic activation takes place – with neutropenia in peripheral blood – which triggers the complement activation and the release of protease and oxygen radicals. Intradialytic neutrophilic activation is responsible for numerous intradialytic and interdialytic complications [2]:

- platelet and red blood cell dysfunction;
- increase of serum lipid peroxidation products;
- reactive oxygen species contribute to amyloid arthropathy;
- the effect of DNA distortion is involved in premature ageing of long-term hemodialysed patients.

Neutrophilic activation during dialysis increases the expression of adhesion molecules with consecutive leucopenia; unlike complement activation and neutropenia, which occur only during dialysis, leucopenia can persist between dialytic sessions [2].

Viral infections in hemodialysed patients

Markers of viral B- and C-hepatitis are more frequent in dialyzed patients than in the general population due to intravenous treatments, transfusions, etc. Frequently, acute viral hepatitis has an anicteric, subclinical evolution. The frequency of HIV-infection in dialysis is comparable to that in the general population [2].

Acquired polycystic kidney disease

It is a complication that occurs in long-term uremia: tubulointerstitial nephropathies, chronic dialyzed patients [2, 10]. It is often associated with improvement of anemia or decreased need for erythropoietin due erythropoietin secretion in cystic walls. Patients with acquired renal cystic disease have, however, an increased risk of developing urothelial neoplasia [2, 10].

Complications induced by the primary renal disease

Residual renal function

Preservation of residual renal function (RRF) after initiating dialysis is proven to have a positive effect on the patients' evolution [11]. Chronic glomerulopathy is associated with early oliguria, while patients with tubulointerstitial nephropathies preserve their diuresis for a longer period [12]; in patients with vascular nephropathies, diuresis is longer preserved if heart failure does not occur [2, 8]. Diabetic nephropathy and heart failure are strong predictive factors for accelerated decline of RRF [13]. Among glomerulopathies, the idiopathic membranous and diabetic glomerulopathies are associated with the greatest risk of rapid RRF loss after dialysis initiation by the persistence of elevated urinary excretion of TGF-β_1 involved in the glomerular sclerosis [14].

Proteinuria has the same harmful effect on the RRF as in the predialytic period; nephrotic proteinuria in chronic dialyzed patients is noted in diabetic nephropathy, mesangiocapillary glomerulonephritis, amyloidosis or focal and segmental glomerulosclerosis [8, 11, 12].

Therapy with ACE-inhibitors in patients with ischemic nephropathy or severe atherosclerosis may suddenly decrease RRF [2, 4].

Bone disease

Because metabolic acidosis is long installed before developing CKD in most tubulointerstitial nephropathies, osteoporosis is noted more frequently and more severe than in other primary renal diseases [5]. Adynamic bone disease is most commonly seen in diabetic patients, but the pathogenesis is still unknown [5, 9]. Patients with analgesic nephropathy have a high incidence of severe secondary hyperparathyroidism [15]. Myeloma, granulomatous diseases bring additional factors to bone damage in chronic dialyzed patients [5, 8].

Recurrences and comorbidities specific to primary renal disease

The diabetic patient with end stage renal disease has a much higher burden of complications in chronic hemodialysis than a non-diabetic one [16]. Even if asymptomatic, the hemodialysed diabetic must be monitored regularly to detect these complications:

▪ a good glycemic control is difficult to achieve as blood glucose is changing during hemodialysis sessions [9];

▪ cardiac and microvascular complications of diabetes continue with extremely high frequency in the context of additional factors brought by hemodialysis: hyperparathyroidism, dyslipidemia, increased atheromatosis, sudden hemodynamic changes during the dialysis session [9]; about 50% of diabetics have asymptomatic ischemic coronary disease [4];

▪ intradialytic hypotension occurs frequently due to autonomous neuropathy [9] and diastolic dysfunction; therefore it is difficult to reach the target "dry weight";

▪ malnutrition is prevalent in hemodialysed diabetic patients: medication may cause anorexia, nausea, appetite loss; diabetic-associated gastroparesis and neuropathy with prolonged diarrhea; congestive heart failure can compete in intestinal malabsorption [9, 16];

▪ diabetic retinopathy has a high risk of worsening or occurring after initiation of hemodialysis due to rapid cyclic changes in plasma osmolarity during the hemodialysis sessions [16];

▪ highly increased risk of urinary tract infections due to diabetic neuropathy [9].

Recurrences of chronic pyelonephritis, frequently due to depressed immunity of dialyzed patients, are accompanied by oliguria; in addition, as a result of decreased efficacy of antibiotics due to tubular concentration defect, prolonged antimicrobial treatment is required with increasing risk of pseudomembranous colitis or other intestinal malabsorption side effects – like nausea, anorexia – which participate to the malnutrition of the chronic dialyzed patient [2, 17]. Sometimes the administration of nephrotoxic antibiotics can not be avoided, causing faster decline of RRF [11].

The recurrence of nephrolithiasis can lead to urinary tract obstruction with secondary septicemia and reduced RRF [17].

Relapses of chronic glomerulopathies are accompanied by proteinuria – which accelerates the decline of RRF and increases the risk of malnutrition or hypertension and oligoanuria that can enhance/promote cardiac failure [8]. In chronic hemodialysed patients, pathogenic therapy is futile and may be accompanied by severe side effects; only ACE inhibitors may be administered for their antiproteinuric action [2, 8].

In most patients with ESRD, clinical and serological activity of systemic lupus erythematosus (SLE) attenuates [8, 18]. However, numerous studies have shown that in the first year after initiation of dialytic therapy, an exacerbation of SLE activity is noted, from reasons still unknown [19, 20]; therefore, most renal transplant programs recommend to undergo a period of dialysis of 3–12 months. The presence of antiphospholipid antibodies appears to correlate with lupus disease exacerbation after initiating dialysis [8, 20]. Diagnosis of extrarenal manifestations of lupus – pleurisy, pericarditis, ascites, myositis, mental disorders, etc., is a challenge for the nephrologist; decreased serum complement characterizes the reactivation of lupus disease, but in clinical practice, pathogenesis may be multifactorial [8, 19].

The therapy of lupus disease exacerbation has many risks [8]:

▪ NSAIDs increase the risk of occult or manifested gastrointestinal bleeding when concurrent heparin is used during dialysis sessions;

▪ corticosteroids therapy may lead to severe complications like gastrointestinal bleeding, gastric or colonic perforation, pancreatitis, myositis, osteoporosis;

▪ immunosuppressive agents worsen immune depression with increased risk of neutropenia, bacterial infections, oral ulcerations, candidiasis.

Clinical picture of scleroderma dialyzed patients may complicate with esophagus motility disorders, gastrointestinal bleeding, pulmonary fibrosis with severe secondary pulmonary hypertension, severe arterial hypertension [8].

Chronic hemodialysed patients, having ischemic nephropathy or nephroangiosclerosis as primary renal disease, develop, from early stages, cardiovascular complications: heart failure, arrhythmias, cerebral or coronary stroke, myocardial or mesenteric infarction.

Complications of autosomal dominant polycystic kidney disease are not influenced by initiation of hemodialysis: infection of cysts, pyelonephritic episodes, urinary tract obstruction by giant cyst, hematuria secondary to cyst rupture into the urinary tract, retroperitoneal bleeding by rupture of a cyst [10]. Therapy of infectious complications is difficult because of the poor concentration of antibiotics in renal interstitium or at cysts level; infection often progresses to septicemia, imposing nephrectomy. Surgical intervenetions are required also in severe hemorrhagic complications (prolonged macroscopic hematuria, retroperitoneal hematoma or retroperitoneal hemorrhage), being accompanied by high risks in chronic dialysis patient. Hemodialysis may even increase the risk of specific complications of polycystic disease; sudden changes of blood pressure and extracellular volume during hemodialysis sessions may precipitate the rupture of a cerebral aneurysm. Eighty percents of patients with autosomal dominant polycystic kidney disease develop, after several years of dialysis, colonic diverticulosis with high risk for diverticulitis, abscesses, colon perforation [10].

Patients with Balkan endemic nephropathy and those with chronic aristolochic acid nephropathy have increased risk of urothelial neoplasia [17, 21, 22].

Chronic hemodialysed patients with primary amyloidosis have a negative prognosis on hemodialysis [8].

Cardiac involvement is associated with high mortality, neuropathy is accompanied by severe dialytic hypotension and the risk of colonic perforation is much higher than in other patients.

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