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Review Article

Common Complications of Hemodialysis: A Clinical Review

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Abstract

Long-term hemodialysis (HD) is the main modality used in the treatment of end-stage renal disease (ESRD). It is associated with a variety of complications such as infection, amyloidosis, anemia, undernutrition, as well as musculoskeletal, and cardiovascular system (CVS) morbidities. CVS complications and HD-related infection are the main causes of death in ESRD patients on HD. Other complications such as stroke, disequilibrium syndrome occur during or post-HD. Missing dialysis sessions may lead to amongst others; death due to sudden cardiac arrhythmias; cardiac arrest due to electrolyte disturbance and/or severe overload. This review discusses the common complications of HD as well as recent advances that are likely to impact its outcome.

Keywords: Amyloidosis, cardiovascular disease, end-stage renal disease, hemodialysis, infection, long-term, renal osteodystrophy, undernutrition

Introduction

Chronic kidney disease (CKD) is a term that represents a heterogeneous group of abnormalities that ultimately result in abnormal kidney structure and function.[1] It is defined as bilateral kidney malfunction that lasts for more than 3 months due to structural damage. This manifests usually as decreased glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, increased kidney profile, deranged electrolytes and minerals, proteinuria, and radiological changes. This is often confirmed by histological examination of kidney biopsied tissue.[2]

CKD is a chronic irreversible disease that is associated with significant morbidity and mortality.[3] Recent reports have suggested that about one and half million cardiovascular disease (CVD)-related deaths, and 25.3 million CVD related morbidity were attributable to impaired kidney function.[4] CKD is categorized into five stages based on the

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GFR [Table 1],[5] with stage 5 (GFR <15 ml/min/1.73 m^2) referred to as kidney failure or end-stage renal disease (ESRD).[5] The causes of CKD vary among the world population. Hypertension and diabetes are the most prevalent causes of CKD and ESRD worldwide.[6] Other causes of CKD in some developing countries include human immune deficiency virus (HIV), hepatitis, chronic glomerular diseases, nephritis, obstructive uropathy, and toxins.[7] Additionally, some countries reported cases of CKD without obvious underlying etiology.[8]

There are multiple complications of HD that include infection (local or systemic), cardiovascular events, ischemic heart disease (IHD), stroke, hypotension, fluid overload, pericarditis), respiratory (pulmonary edema), gastrointestinal (nausea, vomiting), neuromuscular (muscle cramps, restless legs) manifestations. Others such as anemia, metabolic bone disease, itching, sleep disturbance, aching are also common. HD access site complications, psychological disorders (depression, anxiety, and mood changes) can occur after starting HD. Amyloidosis is more common in people who have undergone hemodialysis (HD) for more than 5 years. The tolerability of long-term HD is variable, with suboptimal ability to cope with was reported from a cohort of patients. Peripheral neuropathy, parathyroid hyperplasia, and acquired cystic kidney disease have all been reported in long-term HD patients.[9]

Despite being a common modality for ESRD management, long term HD is not free of complications. HD complications can occur during the dialysis session (Intradialytic), between sessions (Interdialytic), or with long-term dialysis. In this review, the common long-term complications of HD will be reviewed with new updates.

Table 1: Glomerular filtration rate in chronic kidney disease

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

*Relative to adult level. Neither G1 or G2 fullfill the criteria for CKD in the absence of evidence of kidney damage. GFR: Glomerular filtration rate, CKD: Chronic kidney disease

Materials and Methods

This is a narrative non-systematic review of the updated literature on the pathogenesis and management of CKD. The aim is to provide an updated overview on the common long-term complications of HD with a special emphasis on new updates [Figure 1].

Modalities of renal replacement therapy

Although kidney transplantation is the definitive treatment for ESRD, dialysis is still the widely preferred RRT modality for ESRD management than the peritoneal dialysis.[5] Dialysis was introduced as a potential therapy for renal failure in humans in 1924 by Georg Haas. HD involves drawing the blood from an access point in an arterialized venous access to "clean" it from toxins and excess fluids before it is returned to the body via other venous points.[10] Regular long-term HD is usually conducted for 3–4 h per session three times per week. HD is the predominant mode of RRT used all over the world compared to peritoneal dialysis and renal transplantation.[11] Currently, more than 2.5 million adults are receiving RRT, and this number is expected to increase to about 5.4 million by 2030.[12] Despite the wide availability of RRT, it has been reported that in some regions of the world, an estimated 2.3–2.7 million adults die due to a shortage of/or lack of access to RRT.[12] Increased accessibility and wide availability of HD improves ESRD-induced mortality. However, this subsequent decrease in mortality leads to an increase in the number of patients with ESRD who need HD and long-term care, increasing the financial burden on the healthcare systems.[13]

Complications of hemodialysis

Infections

Infection in patients with HD is one of the major reasons for their increased morbidity and mortality. The commonest source of infection in HD is access site-related infections.[14] Other infective foci include pneumonia, skin, and soft tissue, account for about 42%. Further, about 80% of these infections occurred

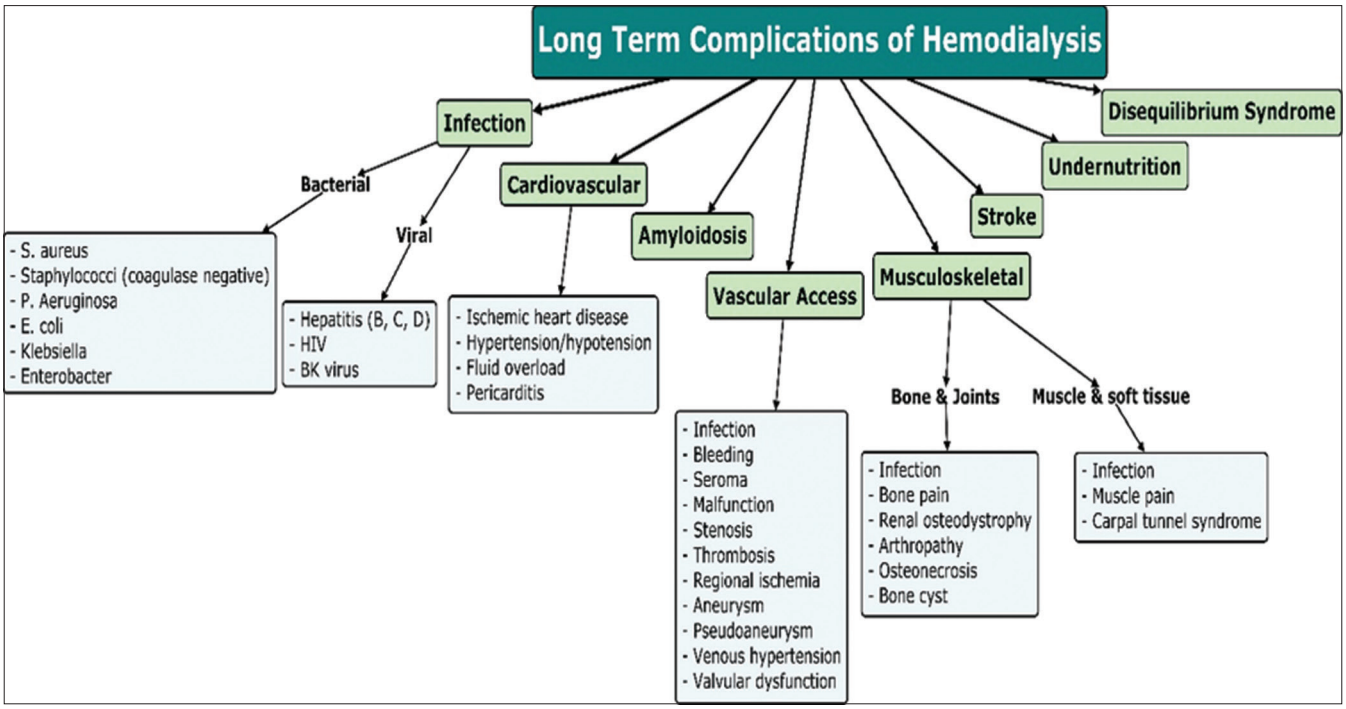

Figure 1: Long term complication of hemodialysis

in the community setting, with 44% needing hospitalization. Infection transmission typically occurs during the start and/or at the end of the HD session. Patients on HD are at a greater risk of infections, particularly blood borne infections, as compared to the general population.[15] This mainly occurs due to contamination from the service providers when strict infection control measures are not implemented. The increased risk is mainly due to improper hand hygiene, cross-contamination of instruments, mishandling of intravenous (IV) medications, inadequate disinfection of dialysis equipment, and failure to adhere to infection prevention and control standard practices.[16] It was reported that health worker infection outbreaks are a threat to patients' safety, morbidity, and mortality.[17] Furthermore, patients undergoing HD have an increased risk of infection due to the negative impact that HD has on both the innate[18] and acquired immunity.[19] In addition, more than 50% of patients with ESRD are hospitalized due to infection. The predominance of infection in these patients was suggested to be due to uremia, while the infection risk is reduced often after managing the uremia [Figure 2].[20] Furthermore, reports support early initiation of renal replacement therapy for ESRD to decrease uremic complications, and to improve the long-term prognosis and quality of life.[21]

Bacterial infection

Staphylococcus aureus, coagulase-negative *staphylococci* (CONS), *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella*, and *Enterobacter* are the most reported causative organisms of bacterial infection. Patients on HD are generally more liable for gram-positive bacteria mainly *S. aureus*.[22] HD access infection causative agents are commonly *S. aureus* and CONS. Surprisingly, gram-negative bacteria are commonly grown from the first sputum cultures of patients with community-acquired pneumonia in HD and CKD patients. It was reported that mortality due to cardiovascular system (CVS) complications appears to be exacerbated by the magnitude of HD-related infection.[23] Although the death rate in patients on HD increases 3 folds due to infection,[23] recent US data has shown a salutary reduction in the death rate attributable to HD-related infection from 43 to 19.4 deaths/1000 patients/year.[24] Previous studies reported that patients who were dialyzed via HD catheter and had hypoalbuminemia, diabetes, anemia, or methicillin-resistant *S. aureus* colonization were at a higher risk of developing septicemia.[22,25]

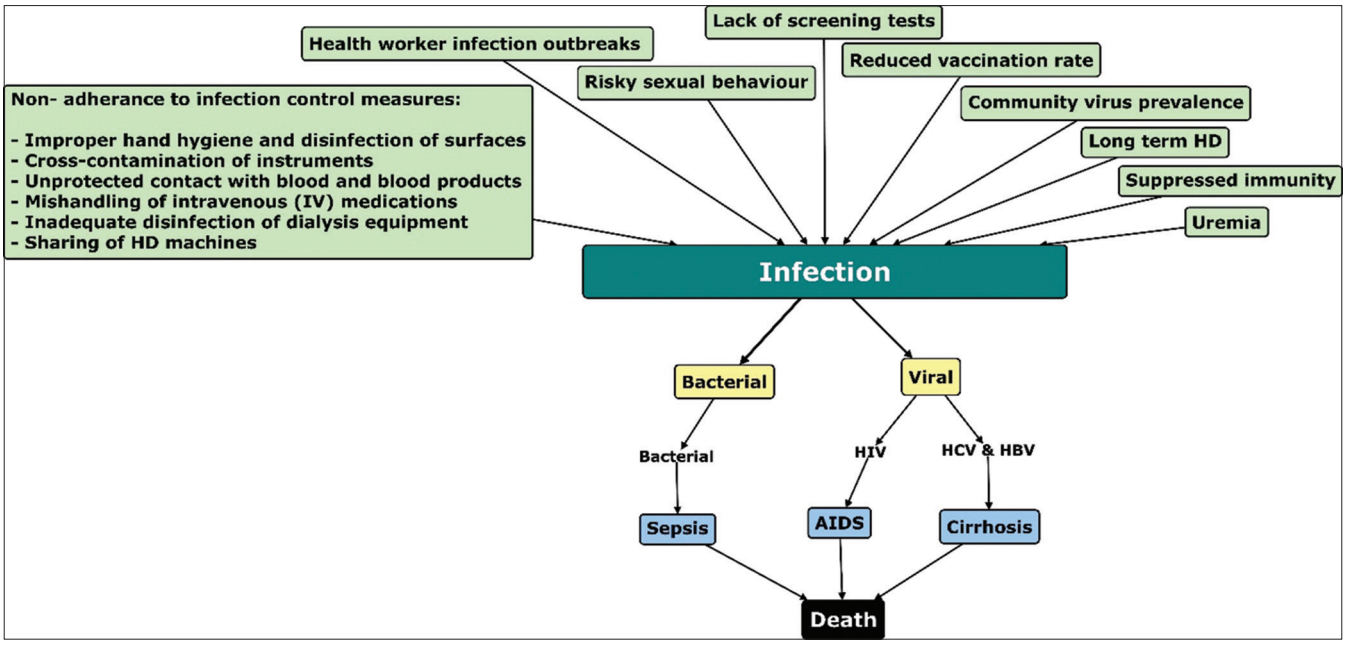

Figure 2: Risk factors for infection in patients on HD. HCV: Hepatitis c virus, HBV: Hepatitis B virus, HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome, HD: Hemodialysis

Viral infection

The commonest viruses in HD patients are hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV,[26,27] which are usually transmitted parenterally.[26] The increased risk of these viral infections in patients on HD is mainly due to suppressed immunity, poorly implemented infection control guidelines, community virus prevalence, and possibly shared machines.[27]

Hepatitis C

HCV is a small RNA virus that was detected in 1989. HCV has 7 genotypes, genotype 1a and 1b are the most prevalent worldwide.[28] According to the World Health Organization (WHO), in 2015, it was globally estimated that around 100 million individuals (1.4% prevalence) had serologic evidence of HCV past or present exposure while 71 million had chronic HCV infection with a prevalence of 1%.[29] Compared to this, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported an overall prevalence of 9.9% in adult patients on HD who were randomly sampled from dialysis facilities in high and middle-income countries. The prevalence ranged from 4.1% in Belgium to 20.1% across the Gulf Cooperation Council Countries.[30] The prevalence of HCV infection in patients on HD can vary widely between different regions of the world, it can range from 1% up to 90% [Table 2]. For example, the prevalence in Northern Europe is <5%, in Southern Europe and the United States around 10%, and in other countries in Northern Africa, South America, and Asia, the prevalence can range between 10% and 70%.[31] The DOPPS study in 2015 showed a reduction in HCV prevalence in patients on HD in the preceding 10–15 years in 5 countries that had participated in the study. These countries include France (14.3%–8.7%), Spain (21.4%–9.1%), Italy (23.1%–12.1%), Japan (19.4%–12.0%), and the United States (11.5%–6.9%). However, the prevalence remained steady in Germany (4.2%–4.5%) and risen in the United Kingdom (2.7%–5.4%).[30] Compared to this, the prevalence of HCV in patients on HD in other Asian and African countries was greater.[30,32-35] [Table 3]. For example, a study from Pakistan reported that HCV seroconversion amongst long-term HD patients was 53%.[32,33] In the Palestine Gaza strip, HCV prevalence was 22%.[32] In Yemen, HCV prevalence among HD patients was about 63%.[34] In Libya, HCV incidence in HD patients was up to 26.3% in different centers with an overall seroprevalence of 16.7%.[35] HCV infection risk among patients on HD is higher than the normal population with an estimated risk of 2% per year especially in third world countries.[31]

Table 2: Prevalence of HCV in patients on hemodialysis in different regions/continents

Continent	Prevalence (%)
Northern Europe	5
Southern Europe	10
North Africa	10-70
South America	10-70
Asia	10-70

Reference[31]

Table 3: Prevalence of hepatitis C virus in patients on hemodialysis in different countries worldwide in order of increasing frequency

Countries	Prevalence (%)
Belgium	4.1
Germany	4.5
United Kingdom	5.4
United States	6.9
France	8.7
Spain	9.1
Japan	12.0
Italy	12.1
Libya	16.7
GCC	20.1
Palestine (Gaza strip)	22
Pakistan	53
Yemen	63

GCC countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates). GCC: Gulf cooperation council

This is mainly due to a lack of screening tests, unprotected contact with blood and blood products, nosocomial transmission, and unprofessional long-term HD.[36] Furthermore, the most common causes of HCV infection in HD centers are due to improper disinfection and cleansing of surfaces, inappropriate care and handling of HD equipment, and unprofessional parenteral drug administration.[37] The increased prevalence of HCV in patients on HD increases the morbidity and mortality amongst HD-HCV infected patients.[28] Further, extrahepatic manifestations of chronic HCV infection such as B cell lymphoma, ocular lesions, dermatitis, sialadenitis, and cryoglobulinemia induced vasculitis were reported, which increases the rate of morbidity and mortality in HD patients.[28]

Hepatitis B

HBV infection causes acute and chronic liver-related pathologies of different clinical phenotypes. HBV transmission occurs through direct contact and body fluids including blood and/or blood products. It was reported that about 2 billion people are infected with HBV globally.[38] In 2015, WHO estimated that about 257 million had chronic HBV infection worldwide, and about a million died due to cirrhosis complications and hepatocellular carcinoma. Despite the increased prevalence of HBV infection, only 27 million (10%) were aware of their infection out of which only 4.5 million were treated as per the WHO 2016 report. The prevalence of HBV varies between world regions, and even within the same region. HBV infection prevalence in the general population is highest in Western Pacific Region (6.2%) and African Regions (6.1%), whereas in the Eastern Mediterranean, South-East Asia, the European region, and Americas, the estimated prevalence was 3.3%, 2.0%, 1.6%, and 0.7%, respectively. Chronic HBV prevalence was <2% in the USA, Canada, and Western Europe, and 2%–7% in Mediterranean countries, Japan, Central Asia, Middle East, and parts of South America, and ≥8% in Western Africa and South Sudan.[4,39] The prevalence and incidence of HBV infection in patients on HD differs by region. In the US, HBV infection incidence was not significantly different in long-term HD patients compared to the general population.[40] However, other world regions had a different reported prevalence of HBV infection in patients on HD, for example, in Asian and Pacific countries 1.3%–14.6%,[41] Brazil 12%.[42] In Sudan, HBV prevalence among patients on HD varies from 0% to 58%.[43] Regular HBV screening especially in patients on HD in addition to the availability of HBV vaccine helps in the reduction of HBV transmission and prevalence.[44] The natural history of HBV infection in patients on HD varies with the time of infection, genotype, and the infected person's region. Harnett *et al*. stated that most new HBV infections in patients on HD had a mild disease course, and persistent elevation of antigenemia and mild liver enzymes, comparing with non-CKD patients.[45]

There are risk factors that can contribute to HBV infection in patients on HD. This includes cross-contamination by using the same dialysis machines for HBV infected and non-infected patients. Although a high-flux dialyzer membrane is efficient in clearing toxins and amyloid proteins,

it may allow the passage of HBV-DNA and transmit the infection. Even though, HD equipment manufacturers claim that the risk is almost null, this is still disputable.[46] HBV transmission in patients on HD is more evident when the appropriate infection control measures are not followed such as in cases of reduced vaccination rate, improper machine disinfection, use of unsterile parenteral drug preparation, and multi-dose shared parental treatments.[34,40] Lastly, it is important to note that ESRD patients on long-term HD who are infected with HBV are still eligible for renal transplantation, hence, prevention, early detection, and treatment increase the probability of transplantation.

Human Immunodeficiency virus

WHO 2020 report revealed that HIV continues to be a major global public health issue, affecting almost 38 million people worldwide. About 1.7 million people were newly infected at the end of 2019. Despite the progress in HIV diagnosis and treatment availability, about 7 million ceased from HIV-related complications, including HIV-related nephropathy in 2019, mainly due to lack of management services availability in some world regions such as Africa and Asia. Risky sexual behavior is the main reason for HIV transmission worldwide. It was reported in 2019 that about 19% of patients infected with HIV were not aware of their infection. In addition, the death rate fell to 51%, and the number of new cases reduced to 39%, mainly due to advancement in HIV therapy and public awareness programs promoting precautionary measures such as safe sexual contact as reported by WHO report 2020.

HIV prevalence among patients on HD is strongly related to its prevalence in the general population. CKD and HD patients' immunity is suppressed, and HIV infection among these patients is not uncommon. In 2000, about 2% of HD patients had either HIV or AIDS, although the incidence was thought to be higher,[47] The prevalence of HIV in HD was heterogeneous; up to 40% of dialysis patients in urban centers had HIV.[48] HIV transmission between patients during HD sessions via HD machines has not been reported in the USA. In addition, private machines for HIV patients are not currently recommended in the US. The risk of patient-to-patient cross-infection and transmission via staff members are unlikely if the disease control and prevention recommendations are implemented.[48]

Antiviral therapy in HD HIV-infected patients improves the survival rate. It was reported that the main risk factors of death in HD HIV patients were the presence of secondary infection and the HIV viremia load. Early initiation of antiviral therapy in HIV ESRD started on HD is strongly recommended.[49] About 1% of HBV-infected patients (2.7 million people) are co-infected with HIV. Conversely, worldwide HBV prevalence among HIV-infected persons is 7.4% which promoted the WHO in 2015 to recommend antiviral treatment for every patient diagnosed with HIV infection, regardless of the AIDS stage.

Hepatitis delta virus infection

Hepatitis delta virus (HDV) requires an accompanying HBV infection to live and cause liver damage.[50] Globally, HDV appears in about 5% of HBV-infected individuals.[51] Patients on HD patients are at a higher risk of HDV infection.[52] HDV infection can present as a co-infection or super-infection. Co-infection is usually acute, whereas super-infection presents as hepatitis B. Super-infection should be considered when an individual with HBV infection deteriorates. HDV has eight genotypes, HDV-1 and HDV-3 are the commonest worldwide. HDV-2 is more common in Japan, Taiwan, Yakutia, Russia, whereas, HDV-4 is higher in Taiwan and Japan, and HDV-5, -6, -7, -8 in Africa.[53] In Iran, HDV-1 was detected in patients on HD patients,[54] and others reported different genotypes in various countries.

Other viral infections

The frequency of hepatitis G virus in normal people is very low, but it is more common in patients with HBV infection, and it is relatively more prevalent in HD patients with uncertainty regarding the pathogenesis.[55] BK virus (BKV) infects up to 90% of the general population, and it occurs more commonly in patients with renal transplant and those on HD. Immune suppression is considered an important risk factor for BKV reactivation in CKD-HD patients.[56]

Cardiovascular disease

CVD is a common complication associated with both CKD and HD. It was reported that the burden of CVD in patients with long-term HD is increased by 5–10 folds compared with the general population.[57] Moreover, CVD complications, mainly IHD, accounted for about 50% of deaths in those patients.[57] In the United States, CVD accounted for more than 50% of deaths in patients with ESRD, with about 38% dying from arrhythmias and cardiac arrest.[58]

Hypertension is not uncommon in patients with CKD and those on long-term HD. The strict control of hypertension in those patients is critical in reducing further kidney damage and heart-related complications. However, hypertension control is difficult in CKD and ESRD and patients often require multiple drug combination. In addition, the high calcium-phosphate product in CKD and ESRD increases the risk of vascular calcification (e.g., coronary artery) and IHD.[59]

Anemia is a well-known complication in ESRD, and it can be due to multiple reasons such as erythropoietin deficiency, hemorrhage, hemolysis, and blood loss during HD. Anemia alone is one risk factor for CVD in ESRD and patients on HD because it increases the risk of cardiomyocyte damage from low oxygen delivery and endothelial dysfunction.[60]

The incidence of acute cardiovascular events such as arrhythmias and cardiac arrest is higher in the first weeks of starting HD mostly due to early systemic inflammatory reactions and endothelial dysfunctions.[61] It has been reported that HD-induced left ventricular regional systolic malfunction correlates directly with serum C-reactive protein and other inflammatory markers before starting HD.[62] At the beginning of HD, complement system activation occurs and activates leukocytes that initiate pro-inflammatory changes in cytokine transcription profiles.[61] Inhibiting complement activation may reduce its downstream effects and thereby decrease the risk of CVD. However, routinely administering heparin during HD has not been shown to effectively suppress complement activation.[63]

HD, via a central catheter or arteriovenous fistula, increases the cardiac output and this, in turn, may increase the risk of regional left ventricle hypertrophy and endocardium ischemia.[64] Conversely, closure of the fistula improves the concentric and eccentric hypertrophy.[65] Furthermore, reducing blood flow to the AV fistula may ameliorate the cardiac structure and hemodynamic changes in some patients undergoing HD.[66]

A low level of triiodothyronine (t_3) occurs in CKD and long-term HD patients. Furthermore, low t_3 is strongly related to left ventricular hypertrophy, and low serum t_3 is a cardiovascular complications marker in CKD and long-term HD patients.[67]

Amyloidosis

Amyloidosis are a rare group of heterogenous disorders characterized by extracellular tissue deposition of abnormally folded proteins called amyloids. Amyloid deposits are formed from soluble proteins which undergo misfolding and subsequently aggregate to form insoluble fibrils leading to progressive organ damage. There are many types of amyloidosis such as hereditary amyloidosis, acquired systemic immunoglobulin light chain (AL) amyloidosis, reactive systemic (AA) amyloidosis, and β2-microglobulin (β2M) dialysis-related amyloidosis. Moreover, amyloidosis can affect different organs such as the brain, liver, kidneys, and joints, hence, leading to a variety of clinical presentations depending on the type, site, and amount of amyloid deposition.[67,68] Mortality and renal prognosis are significantly related to serum AA amyloidosis level. It was reported that the death risk was about 17.7 folds more in patients who had high serum AA concentrations.[69]

Amyloid protein deposition occurring after long-term HD is referred to as dialysis-related amyloidosis. Dialysis-related amyloidosis is a disabling disease characterized by the deposition of amyloid ß$_2$-microglobulin (β_2-M) fibrils in different body tissues of patients with CKD or ESRD.[70] In a healthy individual, β_2-M is filtered by the glomerulus and then reabsorbed and catabolized by the proximal tubules. In patients with ESRD, serum β_2-M concentration rises by about 60-folds

or more. In ESRD patients with HD-dependence, amyloidogenic protein retention has been attributed to dialysis membrane, prolonged uremic state and/or decreased diuresis, advanced glycation end products, elevated levels of cytokines, and dialysate type. Furthermore, cytokines such as interleukin-1, tumor necrosis factors, interleukin-6 production, and complement activation are induced by HD, promoting synthesis and release of β_2-M by the macrophages.[71] The essential method to prevent amyloidosis is by preserving the residual renal function as much as possible to reduce serum β_2-M concentration. β_2-M amyloidosis is a serious complication of long-term dialysis especially after complete loss of the residual kidney function.[70]

HD duration is a major determinant for dialysis-related amyloidosis complications. Amyloidosis in the joints occurs in 21% of patients on HD for <2 years, in 50% at 4–7 years, and in 90% at 7–13 years, and in 100% after 13 years.[72] Similarly, Koch showed a prevalence of 0% after 5 years, about 50% after 12 years, and up to 100% after 20 years of HD.[73] The risk of amyloidosis is higher when HD is conducted by a low flux hemodialyzer compared to a high flux hemodialyzer.[74]

Other important risk factors for dialysis-related amyloidosis include old age, type of the hemodialyzer, dialyzer membrane material, and residual renal function.[75] For example, high-flux membranes and ultrapure dialysis fluid conserve residual renal function and result in better overall clearance of ß2-M compared to low-flux cellulosic membranes.[76] Moreover, patients on HD with a GFR <1 ml/min had a two-fold higher concentration of plasma ß2-M than those with a GFR of 4–5 mL/min.[76]

Vascular access complications

There are many complications associated with vascular access. Major complications include infection, vascular access bleeding, thrombosis, vascular occlusion, stroke, high cardiac output failure, seroma, aneurysm, pseudo-aneurysm in addition to vascular access-related complications like malfunction and stenosis.[2] Infection and septicemia occur especially when HD is conducted via a central catheter. Other complications include venous hypertension, arterial steal syndrome, valvular dysfunction, regional ischemia, neuropathy, hypoglycemia, and early shunt failure.[2] Therefore, early arteriovenous access should be offered to patients with ESRD because it has several benefits such as reducing the failure rate of the fistula and other local complications such as hematoma and seroma.

Musculoskeletal complications

Bone and muscle pain are the main complaints in patients with CKD and ESRD on regular HD and it is inadequately controlled in more than 50% of patients.[77] Musculoskeletal complications are mainly due to the abnormal calcium-phosphate metabolism that is aggravated by HD.[78] Also, several other bone abnormalities can arise from dialysis-related amyloidosis such as destructive arthropathy, osteonecrosis, musculoskeletal infections, and pain before the development of peripheral neuropathy.[79] Bone cysts and carpal tunnel syndrome with flexor tendon contractures and trigger fingers also occur in patients with CKD and long-term HD.[80]

Renal osteodystrophy is a group of bone diseases that occur in patients with CKD. It is characterized by secondary hyperparathyroidism, osteomalacia, osteoporosis, and soft tissue calcification. Dynamic and adynamic bone osteodystrophy in HD patients are two forms of HD-related bone disease. Although osteodystrophy occurs due to secondary hyperparathyroidism and prolonged uremia, it may occur even in normal serum phosphate and calcium concentration.[81] Renal osteodystrophy has been classically related to the severity of hyperparathyroidism effect on the bone. Reduced activated vitamin D leads to hypocalcemia that stimulates parathyroid hormone secretion, increasing serum fibroblast growth factor-23 (FGF-23) level. The direct effect of the FGF-23 role is not established clearly in vitamin D activation in patients with CKD and ESRD. Hyperparathyroidism promotes bone resorption, causing dynamic osteodystrophy.[82] Conversely, adynamic osteodystrophy or a low bone turnover occurs at the early stages when the parathyroid hormone is not significantly high due to treatment with vitamin D, calcium salts, calcimimetics, steroids, and bone remodeling agents.[82] Both

dynamic and adynamic osteodystrophy are reported almost at the same rate in HD-dependent patients.[82]

Stroke

Hemorrhagic and thrombotic strokes occur in patients with CKD and HD-dependency, and its frequencies are often greater during the first weeks of starting HD.[83] Risk factors such as thromboembolism, vascular calcification, hemodynamic instability, and amyloidosis increase the risk of stroke. The mortality in patients with a stroke who are undergoing HD is approximately three times higher compared to patients with CKD who have not started HD.[84]

Stroke incidence in patients with HD increases by 5–10 folds than in the general population, and the mortality increases by 3 folds in patients with CKD who have not started HD.[85,86] Ischemic stroke and CKD are related because both occur concomitantly in old patients with hypertension, hypercholesterolemia, and diabetes. Furthermore, the risk of stroke increases with more deterioration of renal function and progression of proteinuria.[86,87] Moreover, platelet dysfunction that occurs due to uremia and concomitant antiplatelet therapy, uncontrolled hypertension, and dialysis-related anticoagulation increases the risk of hemorrhagic stroke.

Undernutrition

Poor nutrition occurs in patients with CKD, and it is not uncommon in patients with ESRD on HD. The duration of HD is a good predictor of malnutrition and underweight even with adequate protein supplementation, undernutrition is still common in patients on HD.[86] Serum albumin and prealbumin correlates very well with the overall survival rate in CKD and patients dependent on HD.[86] The ESRD-related adynamic bone disease appears to be affected by malnutrition, however, the extent of long-term HD effect on this process remains open to debate. Also, vitamins and mineral deficiencies such as zinc and selenium were reported in patients on long-term HD, and these were thought to occur mostly due to malnutrition and reverse osmosis water purification. Food restriction, appetite loss, nausea are other causes of malnutrition in patients on HD.[88] Malnutrition is reportedly second cause of death after CVD in patients on long-term HD.[89]

Disequilibrium syndrome

Disequilibrium syndrome (DES) is an infrequent neurological condition in patients who have newly commenced HD, although it may still occur in patients on long-term HD.[90] High intracerebral urea levels have been suggested to be the main driver for DES, with additional contribution from inflammatory cytokines, and other putative inflammatory mediators. High intracerebral urea concentration at pre and post-dialysis period leads to fluid movement into the brain (through osmosis), resulting in brain edema.[91] DES often manifests as weakness, dizziness, nausea and vomiting, headache, muscle cramps, behavioral changes, and/or abnormal mental status.[92] DES is usually a short-lasting complication that either improves, but mostly leads to death if it is not properly dealt with. IV saline is sometimes used to raise blood pressure along with mannitol injection to relieve swelling and pressure around the brain.[92] Patients having pre-existing cerebral edema, hyperosmolarity, metabolic acidosis, hypernatremia, hyperglycemia, and those who have active neurological abnormalities are more susceptible to develop DES.[92]

Conclusion

HD is a modality used to treat patients with ESRD symptoms and ultimately improve their quality of life. However, long-term HD is associated with multiple complications. Renal transplantation should be offered to patients at the early stages of ESRD or even before starting RRT to prevent the "legacy effects" of delayed treatment. All HD complications must be sought and managed as early as possible to prevent the increased mortality. It is evident from established and recent reports that most HD-related complications are potentially preventable if managed early, which is especially true for infections, CVD, vascular access complications, and DES. Regular viral screening, vaccination, HD access care, strict infection control protocols, anemia treatment, hypertension and diabetes control, and good follow-up for patients on HD are essential to prevent long-term HD complications. Finally, maintaining residual kidney function is crucial.

Authors' contributions

All authors contributed to the research, literature review synthesis of the themes of the article. They have all participated in drafting, revision and approval of its final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No formal ethical approval is required.

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