Long-term Complications of Hemodialysis

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Abstract:
Hemodialysis is one of the renal replacement therapies, besides peritoneal dialysis and renal transplantation. Although hemodialysis can improve morbidity and mortality in renal patients, it has many complications that occur during the dialysis sessions and/or as long term use of hemodialysis. Hypotension, hypoglycemia, electrolyte disturbances, disequilibrium syndrome, hypocalcaemia etc are common complications occur during dialysis. In long-term dialysis, there are complications as amyloidosis, bone disease, endocrine disturbances, infection, cardiovascular complications, vascular access and nutrition complication. Important long-term hemodialysis complications will be reviewed in this article.

Key words. Hemodialysis, hypotension, muscle cramps, infection transmission, Amyloidosis, HD complications

Introduction:
Renal replacement therapy is an option to treat patients with acute and/or chronic renal failure. There are two treatment options for a patient who develops end stage renal failure with evidence of uremia symptoms. Kidney transplantation is the best option in treating end-stage renal failure (ESRF) patients, however, shortage of donated-organs, pre and post transplantation follow up and worldwide transplantation team availability are obstacles and difficulties in many countries. These reasons have led to the other alternatives of renal replacement therapy modality which is dialysis particularly hemodialysis.

The underlying cause of end-stage renal disease (ESRD) is increasingly changing. In the United States, about 40% of patients have ESRD due to diabetes, hypertension, recurrent urinary tract infection, drug use, glomerulopathies, vasculitic diseases etc. The average age of patients commencing dialysis has risen to 64 years. This increase in starting dialysis age has led to more co-existent diseases that associated with aging as well dialysis complications.

The commonly used modality of renal replacement is hemodialysis (HD). HD for ESRD started in human in 1960 with development of the Teflon arteriovenous shunt by Scribner and co-workers at the University of Washington. The number of patients increased steadily, up to year 2002 about 250,000 in the United State and more than 500,000 patients worldwide were on dialysis.

The most frequent long-term complications in HD patients are related to cardiovascular disease, β2-microglobulin (β2M) amyloidosis, renal osteodystrophy, vascular access, malnutrition, and infection transmission across HD-dependent patients. These complications will be reviewed.

1. Cardiovascular complications
Cardiovascular disease (CVD) is the major cause of death in ESRD patients on regular HD. Atherosclerosis is present in most if not all long-term dialysis patients. CVD in HD patients is 5 to 10 times higher than in general population, and it accounts for at least half of all patients’ deaths. The death in these patients were mainly due to coronary heart disease (CHD). Diagnosis of CHD in chronic dialysed patients requires coronary artery bypass surgery that has more than three times increase in mortality rate in CKD patients than general population.

Hypertension is not common in HD patients and it is usually difficult to control due to many factors. Poorly controlled hypertension is a major risk factor for CVD. Other risk...
factors that may increase the chance of CHD are hyper-phosphatemia and elevated calcium-phosphorus product with calcium deposition in the coronary arteries, the cardiac conduction system, heart valves and blood vessels elsewhere. Anemia, hypertriglyceridemia low HDL-cholesterol increased lipoprotein, insulin deficiency or resistance, high homocystein in blood, endothelial dysfunction, inflammation and elevated C-reactive protein, and smoking are common, and they increase the risk of CHD significantly. Many if not all of these risk factors may have been occurred during the years of chronic renal insufficiency before even starting HD. Reducing the CVD complications in ESRD can be achieved by modifying these risk factors. Hypertension control by drugs is very necessary. Adequate and prolonged HD is recommended, and it should be carried to control hypertension in HD patients. Reducing LDL-cholesterol concentration is of great importance to minimize the risk of myocardial cardiac infarction in non-renal and HD patients with coronary heart disease. Vitamin E has been suggested as a means of reducing oxidative stress and cardiovascular mortality. Achieving lower plasma LDL-cholesterol with Cervastain that has also anti-inflammatory effect may reduce long term HD complications in HD-patients.

Hyperphosphatemia and elevated calcium phosphate product, and the use of calcium based phosphate binders are high risk factors for vascular calcification. Low calcium dialysate content and selective vitamin D analogues use helps to minimize and improve bone and vascular calcification complications.

Anemia is a commonest complication in HD-patients. It is a major risk factor for CVD and increasing mortality in HD patient. Anemia correction by adequate tonic supplements, erythropoietin and adequate HD patients improves cardiovascular dynamics, exercise tolerance and morbidity as well the mortality.

Cardiac disease in HD dependent ESRD is usually managed with ordinary treatment measures of cardiac problems, however, percutaneous transluminal coronary angioplasty, stenting and bypass surgery are indicated in HD patients. These interventional measures have higher risk mortality, recurrence and restenosis than general population.

2. Amyloidosis
β2M amyloidosis deposition begins usually during few months of starting HD. The clinical and radiological amyloid findings appear usually after five years or more of HD. Sternoclavicular and hips joint are commonly the first joints involved, however, any joint can be affected. Severe spinal cord compression due to β2M amyloidosis deposition occurs often after ten years of HD. Amyloidosis deposition at the joints may present clinically by features of periartthritis of the shoulders, carpal tunnel syndrome, flexor tenosynovitis of the hands, stiffness, pain and swelling of other joints, deposits beneath the skin and spondyloarthropathy. After fifteen years of regular HD, β2M amyloid systemic infiltration of visceral organs occurs, but it is usually asymptomatic.

β2M amyloidosis pathology is not well established and poorly understood. It is reported, following successful renal transplantation, amyloid symptoms improve and its progression halts with reduction in plasma β2 amyloid. Others have reported that the available HD modalities can remove some of produced β2M, but it will not reduce the amount of β2M amyloid that can prevent the known amyloidosis complications, even with high-flux dialysis using ultrapure water to produce dialysate.

3. Osteodystrophy
Long-term HD increases osteodystrophy risk. Osteodystrophy is commonly associated with secondary hyperparathyroidism that is characterized by high plasma parathyroid hormone despite of normal serum calcium and phosphate.

Osteodystrophy prevalence in long-term HD patients, together with impaired handling and buffering of calcium loads that accompany secondary hyperparathyroidism is increasing. Hip fractures frequency due to osteodystrophy is more frequent and serious in long-term HD patients than in the matched general population. Dynamic and adynamic bone diseases occur in CKD patients, but their prevalence is more after starting HD.

4. Undernutrition
Undernutrition is often common in HD dependent patients, and time duration on dialysis is a strong predictor of malnutrition.
Patients on HD more than ten year are tending to loss their body weight despite adequate protein intake. Although the underlying cause of malnutrition is unclear, it may be due to chronic metabolic acidosis, or to decreased physical activity as a result of β₂M-amyloidosis rather than the reduction in energy expenditure. It had been reported that the survival rate is correlated with serum albumin and prealbumin levels. Occurrence of adynamic bone disease also appears to relate to malnutrition, although it is unclear whether this is a causal relationship, or whether both conditions are characteristic of long-term HD survivors. Zinc and selenium deficiency have been reported in chronic dialysis patients which is mostly due to malnutrition and reverse osmosis water treatment may has role.

5. Vascular Access
Vascular access of HD should be planned as early as possible, especially in elderly and diabetic patients. Native arteriovenous fistula (AV) is always recommended whenever possible. Early dialysis must be initiated, while it reduces the frequency of complications, but may or may not improve patient survival during the first few months of treatment. Complications of vascular access as infection, malfunction, stenosis, disfigurement etc are major concern, and can lead to inadequate dialysis.

Hemodialysis vascular access infection is common causes for hospitalization in HD patients, and can cause serious complications. In less serious catheter and graft infections, it is sometimes possible to eradicate the infection with several weeks antibiotics course. The persistence of fevers, an elevated number of white blood cells in the blood, or constitutional symptoms, all can indicate antibiotic treatment failure, and that indicates the vascular access should be removed.

AV grafts are less likely to become infected than catheters and non-native fistula. When AV grafts become infected, it is usually due to hematoma formation that spreads to graft material. So, HD patients should avoid prolonged use of hemodialysis catheters, because they are associated with frequent and serious infections. Strict hygienic sterile methods should be applied to reduce the risk of the infection.

6. Infection transmission
Dialysis has led to decrease mortality and morbidity in ESRD patients, but it predisposes these patients to blood born infections, partly due to an abnormal immune system function in CKD patients and in dialysis dependent ESRD patients. In dialysis patients, white blood cells count may be normal, but the white blood cells are typically not functioning normal. This abnormality has led to more risk of staphylococcus infection.

Lymphocytes are primarily involved in protection against infections caused by viruses and fungi. HD dependent patients have increased incidence of viral and fungal infections due to lymphocyte malfunctioning. Simple viral infections as influenza occurs, but also serious conditions such as shingles and hepatitis are not common. Hence, vaccinations against these infections decrease the severity of these viral infections.

The spread of infectious agents from the dialysis machine or other dialysis related procedures to the patient is unusual in the setting of current infection control policies, but it does rarely occur. Dialysate fluid might be contaminated with an infectious agent, and theoretically can transmit infections, although the dialyzer membrane material is an effective barrier to the spread of these agents from the machine to patient's blood. Infection related to the dialysis treatment is unusual, but it can occur during the put-on or take-off process where infectious agents can be introduced into the patient's vascular access due to improper sterile technique. Therefore, it is important for patients to become familiar with and he/she should insist that sterile technique must be used during the beginning and ending of dialysis treatment.

Various studies have shown a higher prevalence of HBV, HCV and HIV in HD patients than in the general population. The increase of these viruses infection may be due to dialysis machines sharing, inappropriate preparation of parenteral drugs and inadequate infection control methods in dialysis units. Blood transfusion needs and the suppressed immunity of patients may also have role in these viruses' transmission.

HCV infected patients are usually asymptomatic. This is leading to higher HCV transmission risk because these patients and
the HD staff was unaware about the infection transmission risk, and this may not made them strictly compliant to the standard infection measures. It has been suggested that HCV transmission in dialysis units is mainly a result of environmental contamination, therefore, currently dedicated machines are not commonly recommended for HCV-positive patients. Furthermore, due to the lack of an effective HCV-vaccine has led to higher risk of chronic HCV hepatitis in HD patients.

A determined average prevalence of HCV in hemodialysis patients in Iran were 13.2%, while others reported lesser prevalence in other areas of Iran.\textsuperscript{45} Alavian et al\textsuperscript{44} (2012) reported, the average rate of HCV infection in HD patients in 12 areas in Iran has been estimated about 7.6%, and it has been concluded that Iran is among the low-prevalence countries in terms of HCV in hemodialysis patients.\textsuperscript{45}

Prevalence of hepatitis virus infections seems to be higher in underdeveloped and developing countries than in developed countries. The prevalence of HBV and HCV in Palestine has been reported to be 8.1% and 22% respectively.\textsuperscript{46} In Yemen, the HCV prevalence rate was 62.7%.\textsuperscript{47} In the Middle East, the rate of HCV infection in HD patients is higher; in Jordan, Syria (28%, 48% respectively).\textsuperscript{48,49} High incidence of HCV has been noted in some countries as India where 83% prevalence is reported in dialysis patients,\textsuperscript{50} 71% prevalence reported in Venezuela\textsuperscript{51} and 46% in Saudi Arabia.\textsuperscript{52} A low prevalence of 5.72% was noted in Switzerland,\textsuperscript{53} while in France it was 7.7%.\textsuperscript{54} These differences might be due to the time period elapsed on hemodialysis, dialysis machine availability and good strict compliant of staff and patients to infection control rules.

HBV infection was also found in 7% of HD patients in the Kerman Province which is similar to other studies in other areas of the country. In the Khuzestan Province, 5.1%,\textsuperscript{55} and in Uromiye 6.5%\textsuperscript{56} of the hemodialysis patients had positive HBs-Ag. The prevalence of positive HBs-Ag in the general population of Iran has been estimated to be 2.6%.\textsuperscript{57} These findings also support the higher prevalence of HBV in HD patients. The role of occult hepatitis B infection in the spread of infection may need more attention. Despite negative HBs-Ag, these patients may have positive HBV-DNA and may infect others.

Prevention of CKD and its late consequences should be the ultimate goal of health-care providers. In order to improve the survival and reduce the morbidity in all CKD patients, it is essential to optimize the pre-ESRD care of patients with chronic renal insufficiency. It is documented that strict blood pressure control with ACE-inhibitors, ARBs or other hypertensive medical therapy,\textsuperscript{59} protein restriction,\textsuperscript{60} tight control of diabetes,\textsuperscript{50,62} anemia correction by improving nutrition and erythropoietin\textsuperscript{63} can reduce or may delay the need for dialysis. Lipid profile control is also an important issue to prevent complications - especially the cardiovascular complications that may occur in CKD patients either pre- or after HD.\textsuperscript{64} Moreover, Focus on the prevalence of HBV, HCV hepatitis and HIV in HD centers and the determination of their risk factors helps health planners to establish more effective measures to reduce their prevalence and recirculation, mortality and ultimately reduce rates of morbidity.\textsuperscript{65} These tasks can be achieved by strict adherence to infection control measures - routine screening of donated blood products, separation of HBV, HCV and HIV dedicated dialysis machines, HBV vaccination and periodic testing for HBV, HVC and HIV infection markers. Patients’ compliance and staff to follow national and international recommendations must be strictly applied.

7. Conclusion:
Considering the varied factors that may affect the morbidity and mortality of HD patients and the steady increase in patients with CKD on HD worldwide, it is clear that there is a huge need for more research to assign the best way to diagnose and to treat kidney diseases at early stages to prevent late complications of CKD and HD. Further collaborative national and international multicenter outcome researches are needed to establish the preventive and treatment guide lines that can be helpful and positively affect morbidity and mortality in kidney diseases and the long-term complications of dialysis.

8. References:
