Effect Of Serum Potassium Level On Hemodynamic Stability During The Hemodialysis Session.

Thesis

Submitted for partial fulfillment of Master Degree in Nephrology.

BY

Heba Mahmoud Lotfy Elsayed

Diplome of Internal Medicine

Faculty of Medicine - Ain Shams University.

Under supervision of

Prof.Dr. Mohammed Mahmoud Abd Elghany

Professor of Internal Medicine and Nephrology

Faculty of Medicine - Ain Shams University

Dr.Cherry Reda Kamel

Assistant professor of Internal Medicine and Nephrology

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

2017

Contents:

List of figures

List of Tables

Cardiovascular Disease in Hemodialysis Patients

Cardiovascular disease (CVD) is a most common complication and a chief cause of death in patients with end stage renal disease (ESRD) accounting for 45% to 50% of causes of death in ESRD patients. In ESRD patients, mortality due to CVD is 10~30 times higher than in the general population. 80% patients on maintenance homodialysis (MHD) had cardiovascular complication. **(*Li and Wang ; 2013)***

1) Risk factors

A)Traditional risk factors

1)HYPERTENSION

Hypertension is a common complication in patients with chronic kidney disease. The incidence of hypertension grows along with the decrease in glomerular filtration rate (GFR). It was reported that the incidence of hypertension in patients with GFR less than 60 ml/min was 50%-75%. However, the incidence of hypertension was extraordinarily higher in MHD patients.**(*Batlle et al ;2003*)**

Hypertension is a significant risk factor for cardiovascular disease in MHD patients. **Foley et al*(1996)*** found that with each 10 mm Hg increase of BP in MHD patients, the risk of LVH increased by 48%, ischemic heart disease increased by 39% and congestive cardiac failure increased by 44 %.

The causes of hypertension in MHD patients are miscellaneous, including volume overload activation of the RAS ,sympathetic hyperactivity . MHD patients always need to be treated with combinations of 3 or more categories of antihypertensive drugs.***(Neutel;2010)***

2) SMOKING

Smoking is associated with progression early-stage CKD patients, and may well adversely impact residual renal function in dialysis patients. Smoking strongly associates with incident heart failure, incident peripheral vascular disease, and all-cause mortality.***(Nagasawa ;et al;2012)***

3) DIABETES

Diabetics are at higher risk for acute coronary syndromes. Additionally, there is increased prevalence of heart failure. Poor blood glucose control is associated with increased mortality in dialysis patients. ***(Dyck et al;2012)***

4)DYSLIPIDEMIA.

Dyslipidemia is a well-established metabolic disorder in dialysis patients. A recent study found that a significant increase of serum triglycerides ($p= 0.002$), lipoprotein (a) ($p = 0.001$) and C Reactive Protein ($p = 0.008$) was observed in patients when compared with healthy controls. A significant decrease of serum total cholesterol ($p=0.01$), HDLcholesterol ($p<0.001$), LDL-cholesterol ($p=0.005$) and apolipoprotein AI ($p<0.001$) was also observed in patients. ***(Kharrat et al;2012)***

A study of cholesterol metabolism in patients with hemodialysis in the presence or absence of coronary artery disease showed that HD patients showed lower cholesterol concentrations than non-HD patients, and, as compensation, their cholesterol absorption might be accelerated.

However, higher cholesterol synthesis, which was correlated with higher BMI, might be an independent predictor for the presence of coronary artery disease in HD patients .***(Saku et al;2012)***

A)Cholesterol

In dialysis, the relationship of total or low-density lipoprotein (LDL) cholesterol to mootality is U-shaped; patients with LDL cholesterol levels above 100 mg/dL (2.6 mmol/L) are most likely at increased risk for adverse cardiovascular outcomes, but low levels, probably indicating malnutrition, also are associated with higher mortality rates.

Despite frequently reduced levels total and LDL cholesterol, atherogenic lipoprotein remnants and lipoprotein (a) are generally increased and high-density lipoprotein (HDL) cholesterol levels are generally reduced, likely contributing to CVD risk.

On the other hand, Dialysis per se have neutral effects on serum lipid profile, however, certain dialysis-related parameters may have significant affect on lipoprotein metabolism and modify the feature of dyslipidemia in hemodialysis (HD) patients.

These parameters include; membrane used in dialyzer (high flux vs. low flux), type of dialyzate (bicarbonate *vs.* acetate), anticoagulant (heparin) and the phosphate-binder (sevelamer hydrochloride). The use of high-flux polysulfone or cellulose triacetate membranous instead of low-flux membrane is associated with a significant reduction in triglyceride levels and an increase in apolipoprotein Al and HDL-cholesterol levels. ***(Blankestijn et al;1995)***

The use of bicarbonate dialyzate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate.***(Jung et al;1995)***

Chronic use of heparin as an anticoagulant releases lipoprotein lipase from the endothelial surface which may result in lipoprotein lipase depletion

and defective catabolism of triglyceride rich-lipoprotein. Finally sevelamer hydrochloride significantly reduces the concentration of total cholesterol and apolipoprotein-b in HD patients. ***(Chertow et al;2002)***

B)HYPERTRIGLYCERIDEMIA

Nearly one third of dialysis patients have hypertriglyceridemia, defined by levels above 200 mg/dL (2.26 mmollL), with levels occasionally up to 600 mg/dL (6.8 mmol/L). The predominant underling cause is a deficiency of lipoprotein lipase, resulting in reduced lipolysis of triglyceride (TG)-rich very low-density lipoproteins (VLDLs) and yielding high quantities of atherogenic remnant lipoproteins. Enrichment of LDL particles with triglycerides also suggests partial deficiency of hepatic lipase.***(Li and Wang;2013)***

B)Non traditional risk factors:

1) CHRONIC VOLUME OVERLOAD

Volume overload is a common manifestation in MHD patients. Volume overload can increase returned blood volume, cardiac afterload, and left ventricle wall pressure.***(Munoz Mendoza et al;2011)***

In early stage, the cardiac changes of adaptive ventricular chamber enlargement and myocardial hypertrophy induced by volume overload maybe reversible. Removal and control of excess fluid with dialysis is considered critical for protection against cardiovascular sequelae. A recent

Chinese study found that antihypertensive agents including beta-blockers may influence hemodynamics, which may limit fluid removal during hemodialysis .***(Cheng et al;2012)***

2) ANEMIA

Anemia is predictive of morbidity and mortality from cardiovascular causes in patients with CKD or on dialysis .It leads to reduced oxygen delivery to tissues, causing organ dysfunction. It also causes hemodynamic adaptations including a high cardiac output state to maintain adequate tissue oxygenation leading to left ventricular dilatation and hypertrophy .***(Weiner et al;2005)***

However, at the present time, correction of anemia to hemoglobin levels above 13 g/dL (130 g/L) has not been associated with a cardiovascular or survival benefit. Maintenance of hemoglobin levels above 11 g/dL (110 g/L) is currently recommended and may prevent further progression of LVH.

Guidelines for the management of anemia and iron deficiency in chronic hemodialysis (HD) patients have been developed to standardize therapy and improve clinical outcome. But a recent Dutch study found that compliance with anemia targets in stable HD patients was poor and showed a wide variation between treatment facilities. ***(Grooteman et al;2012)***

3)INFLAMMATION

The role of chronic inflammation as a putative cause of high mortality in ESRD has attracted considerable interest during the last decade. It has been hypothesized that in addition to its direct pro-atherogenic effects, chronic inflammation may serve as a catalyst and in the toxic uremic milieu

may modulate the effects of concurrent vascular and nutritional risk factors .***(Carrero and Stenvinkel;2009)***

ESRD has become a prototype for chronic inflammation. There is consistent evidence that CRP and pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α are risk factors for atherosclerotic complications and predict death and adverse cardiovascular outcomes in these patients.***(Barany et al;2002)***

Schwarz et al. have shown that coronary atherosclerotic plaques in ESRD patients are characterized by increased medial thickness, infiltration by and activation of macrophages and marked calcification. Available evidence suggests that heavily calcified and inflamed plaques contribute to excessive cardiovascular risk in ESRD patients. ***(Schwarz et al;2000)***

Levels of CRP increase as the renal function deteriorates and are particularly high in patients with ESRD. As many as one third to one half of patients with ESRD have CRP levels in the very high-risk category, and CRP continues to be an excellent predictor of adverse outcome in this population .***(Stenvinkel and Alvestrand ;2002)***

4)OXIDATIVE STRESS

Numerous factors in the dialysis patient increase oxidative stress (OxStress). These include inflammation (as marked by elevated C-reactive protein), malnutrition (by reducing antioxidant defenses), uremic toxins, and, potentially, the dialysis procedure itself. Many protective mechanisms are

impaired, including reduced plasma protein-associated free thiols such as glutathione. This may magnify the impact of OxStress in the dialysis population. OxStress is recognized as acritical factor in the development of atherosclerotic cardiovascular disease (ACVD) .***(Singh and Jialal ; 2006)***

According to the oxidation hypothesis of atherosclerosis, low-density lipoprotein (LDL) in its native state is not atherogenic. LDL must undergo oxidative modification before it can contribute to the initiation and progression of atherosclerosis. Data from animal models of atherosclerosis, both diet-induced and genetically altered models, have demonstrated the presence of oxidized LDL (oxLDL) in plasma as well as in atherosclerotic lesions. Presence of oxLDL, autoantibodies against malondialdehyde-modified LDL, and of LDL-IgG immune complexes has also been reported in human plasma and human atherosclerotic lesions .***(Le NA;2009)***

5) HYPERHOMOCYSTEINEMIA

Homocysteine levels increase dramatically as kidney function declines, with as many as 80% of dialysis patients classified as having hyperhomocysteinemia. In dialysis patients, some but not all studies suggest that hyperhomocysteinemia is independently associated with CVD mortality. Nutritional status confounds these analyses, since better nourished patients tend to have higher homocysteine levels. The relationship between

homocysteine levels and cardiovascular disease was described initially by observational studies, which may overestimate the effect of this relationship. Two meta-analyses of epidemiologic studies suggested that reduced homocysteine levels could lower the risk of coronary heart disease, stroke, and cardiovascular disease. ***(Boushey, et al;1995)***

However, **Bazzano et al** concluded that folic acid therapy did not significantly contribute to cardiovascular disease, stroke, or myocardial infarction. ***(Bazzano et al;2006)***

2) Cardiovascular Diseases in hemodialysis patients:

A)Coronary artery disease and Myocardial infarction (CAD AND MI):

Epidemiology and pathophysiology

The incidence and severity of obstructive CAD increases as glomerular filtration rate (GFR) declines. CAD shows a pattern of diffuse multi-vessel involvement with coronary calcification; ***(Chonchol et al;2008)***

Small angiographic studies suggest that this incidence exceeds 50% in unselected CKD 5D patients. Among patients with CAD, concomitant CKD portends a worse prognosis. Cardiovascular morbidity and mortality are inversely and independently associated with kidney function,particularly at estimated GFRof15 ml/min per 1.73m2.***(Gibson et al;2003)***

Standard cardiovascular risk factors are common in CKD, but do not fully explain the high incidence of cardiovascular events or increased mortality rates; their association with cardiovascular outcomes is attenuated or even reversed at the most advanced CKD stages. Inflammation and oxidative stress have been linked to the pathogenesis of plaque formation and plaque rupture; both are associated with worse cardiovascular outcomes. The role of mineralocorticoid excess in the development of cardiovascular complications is increasingly recognized. Recent studies have implicated disordered mineral and bone metabolism in the pathogenesis of coronary disease and CVD in CKD patients. ***(Briet and Schiffrin;2010)***

Diagnosis

Although early detection of coronary plaque may permit risk factor modification and pharmacological intervention, the increased prevalence of CAD among CKD patients diminishes the negative predictive value of diagnostic studies in this population. CKD patients are underrepresented in cohort studies evaluating the diagnostic sensitivities and specificities of non-invasive tests. Exercise electrocardiographyis limited by lack of specificity of the ST-segment response and by inability of many CKD patients to

exercise to a diagnostic workload. ***(Karthikeyan and Ananthasubramaniam;2009)***

Diagnosis of acute coronary syndrome may also be problematic in CKD. The classic triad of ischemic symptoms, elevated cardiac biomarkers, and electrocardiographic changes is frequently absent in CKD patients. ***(Herzog et al;2007)***

LVH with a strain pattern may mask diagnostic ST depression.Conversely, creatine kinase MB isoform and cardiac troponins (cTns) may be elevated in the absence of true myocardial necrosis, possibly because of myocardial apoptosis or small vessel disease. ***(Freda et al;2002)***

Prevention

The altered relationship of typical risk factors with cardiovascular outcomes and the routine exclusion of patients with advanced CKD from most clinical trials testing CVD therapies engender doubt about the relevance of existing standards of care to these patients. Evidence of the efficacy of glycemic or blood pressure (BP) control or lifestyle modification to reduce cardiovascular events in patients with advanced CKD remains limited. Strict glycemic control may not benefit CKD 5D patients. ***(Williams et al;2010)***

Randomized data on the efficacy of specific BP goals in CKD 5D patients are lacking. The labile nature of BP and the absence of clear associations between hypertension and adverse cardiovascular outcomes in

CKD 5D preclude definitive recommendations about BP control. Lifestyle modifications have not been widely studied in CKD patients; in a small trial, multifactorial intervention that included smoking cessation was not associated with significant cardiovascular benefits.

(Agarwal;2010)

Data are sparse regarding efficacy of prophylactic aspirin in advanced CKD. Subgroup analyses of randomized trials have demonstrated convincing cardiovascular risk reduction from daily aspirin in individuals with estimated GFR45 ml/min per 1.73m2, including CKD 5D patients, despite higher incidence of bleeding in CKD patients.**(*Jardine et al;2010)***

With release of initial results from the SHARP (Study ofHeart and Renal Protection) trial, statins may now be the best-studied medical therapy in the context of advanced CKD. Nevertheless, debate continues regarding their appropriate role. A subgroup analysis of several randomized clinical trials suggests benefit in patients with moderate CKD. ***(Tonelli et al;2004)***

Conversely, two large trials comparing statins with placebo in hemodialysis patients did not demonstrate benefit.***(Fellstrom et al;2009)***

Treatment

Randomized data on treatment of acute MI in CKD patients are sparse, but treatment approaches using aspirin, clopidogrel, b-blockers, and angiotensin-converting enzyme inhibitors (ACEIs)/ARBs (angiotensin receptor blockers) seem to have similar benefits in CKD and non-CKD patients. ***(Keltai et al;2007)***