The Effect of Different Dialysate Calcium Concentrations on Parathyroid Hormone Levels in End Stage Renal Disease Patients on Regular Hemodialysis

Thesis

Submitted for Complete Fulfillment of Master Degree in Internal Medicine

Submitted by

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Cairo University
2012
بسم الله الرحمن الرحيم

"وقل رب زدني علماً"
ABSTRACT

Background: Calcium Concentrations in the dialysate can be customized depending on the current and targeted serum Ca levels as well as the desire to maintain hemodynamic stability during dialysis and prevent the progression of secondary hyperparathyroidism

Objectives: The aim of this work is to investigate the relative role of Different Dialysate Calcium Concentrations on Parathyroid Hormone Levels and Cardiovascular stability in ESRD patients on regular hemodialysis

Methods: A total number of 80 patients with end stage renal disease (ESRD) on regular haemodialysis (HDX) for more than 1 year, were divided into 2 groups: Group (A) : consists of 40 Patients who were dialyzed with low calcium dialysate (LdCa, 1.25 mmol/L) and Group (B) : consists of other 40 Patients who were dialyzed with high calcium dialysate (HdCa, 1.25 mmol/L), . Dialysate composition was otherwise the same, All routine labs were done together with ECG and transthoracic echocardiography

Results: The mean value ± SD of: Total serum Calcium of Group A (7.93 ± 1.008) mg/dl and Group B (8.518± 1.01) mg/dl.(p< 0.05). Ionized Calcium of Group A (1.08 ± 0.09) and Group B (1.139± 0.1) mmol/l.(p< 0.05). Serum Parathyroid Hormone of Group A (492.75 ± 282.57) pg/ml and Group B (389.33 ± 223.240) pg/ml.(P value :0.073).

Intradialytic Hypotension was observed in 22.5 % of Group A patients while observed in 15 % in Group B (P: 0.39) .Aortic valve calcification was present in 22.5% in Group A patients while present in 42.5 % in Group B (P:0.065) while Mitral valve calcification was present in 25 % patients in Group A patients while present in 42.5 % in Group B (P:0.09), Both valve calcification were present in 7.5 % of Group and 17.5% of Group B (P:0.176) while No valve calcification was observed in 60% of Group A and 32.5 % of Group B (P: 0.014)

Conclusion: A lower dialysate Ca concentration of 1.25 mmol/L will offer much less risk of Ca loading and resultant hypercalcemia and calcification However, may predispose to cardiac arrhythmias and hemodynamic unstable dialysis sessions with intradialytic hypotension while A Higher dialysate Ca concentration of 1.75 mmol/L is effective in Suppression of hyperparathyroidism ,However may predispose to hypercalcemia, valvular calcification, and oversuppression of parathyroid hormone

Keywords: Parathyroid Hormone - Dialysate Calcium – Valvular Calcification
First, thanks are all due to Allah for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

It was an honor to work under the supervision of eminent professors, who lent me their whole hearted support and immense facilities as is their usual with their juniors. To them, I owe more than I can record.

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<td>adynamic bone disease</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Angiotensin Converting Enzyme Inhibitor</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>ARBS</td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>AVC</td>
<td>Aortic valve calcification</td>
</tr>
<tr>
<td>BAPTA</td>
<td>bis(o-aminophenoxy)ethane-N, tetraacetic acid</td>
</tr>
<tr>
<td>BB</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>Ca</td>
<td>Calcium</td>
</tr>
<tr>
<td>Ca MB</td>
<td>Ca mass balance</td>
</tr>
<tr>
<td>Ca x P</td>
<td>Calcium Phosphorus product</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery disease</td>
</tr>
<tr>
<td>CaR</td>
<td>calcium sensing receptor</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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<tr>
<td>CI</td>
<td>Collapse Index</td>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>CKD-MBD</td>
<td>Chronic kidney disease –mineral bone disorder</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>dCa</td>
<td>Dialysate calcium</td>
</tr>
<tr>
<td>DCOR</td>
<td>Dialysis Clinical Outcomes Revisited</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocaodiography</td>
</tr>
<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drug association</td>
</tr>
<tr>
<td>FGF 23</td>
<td>Fibroblast growth factor 23</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>gm</td>
<td>Gram</td>
</tr>
<tr>
<td>HD</td>
<td>Hemodialysis</td>
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<tr>
<td>HdCa</td>
<td>High calcium dialysate</td>
</tr>
<tr>
<td>HDF</td>
<td>Haemodiafiltration</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>Hydroxy-3-methylglutaryl coenzyme A</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>I ca</td>
<td>Ionized Calcium</td>
</tr>
<tr>
<td>IDH</td>
<td>Intradialytic Hypotension</td>
</tr>
<tr>
<td>IDWG</td>
<td>Interdialytic weight gain</td>
</tr>
<tr>
<td>IDWG</td>
<td>Interdialytic weight gain</td>
</tr>
<tr>
<td>IU</td>
<td>International unit</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>K/DOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>LdCa</td>
<td>Low calcium dialysate</td>
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<tr>
<td>LDL</td>
<td>Low density lipoproteins</td>
</tr>
<tr>
<td>LHD</td>
<td>Long haemodialysis</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<tr>
<td>LVH</td>
<td>Left ventricular Hypertrophy</td>
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<tr>
<td>MAC</td>
<td>Mitral annular calcification</td>
</tr>
<tr>
<td>Mg</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Mg/L</td>
<td>Milligrams/Litre</td>
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<tr>
<td>MGP</td>
<td>Matrix Gla protein</td>
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<tr>
<td>ml</td>
<td>milliliter</td>
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<tr>
<td>Mmol/l</td>
<td>Millimolar/liter</td>
</tr>
<tr>
<td>Na</td>
<td>sodium</td>
</tr>
<tr>
<td>NDHD</td>
<td>nocturnal daily haemodialysis</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non steroidal anti inflammatory drugs</td>
</tr>
<tr>
<td>Po4</td>
<td>Phosphours</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>QB</td>
<td>Pump speed</td>
</tr>
<tr>
<td>rHuEpo</td>
<td>recombinant human erythropoietin</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDHD</td>
<td>Short daily haemodialysis</td>
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<tr>
<td>SHD</td>
<td>Standard haemodialysis</td>
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<tr>
<td>SHPT</td>
<td>Secondary hyperparathyroidism</td>
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<tr>
<td>SMC</td>
<td>Smooth muscle cell</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Science</td>
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<td>T ca</td>
<td>Total Calcium</td>
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<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------</td>
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<tr>
<td>TPN</td>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USRDS</td>
<td>United States renal data system</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D receptor</td>
</tr>
<tr>
<td>VDRAs</td>
<td>vitamin D receptor activators</td>
</tr>
<tr>
<td>VSMCs</td>
<td>vascular smooth muscle cells</td>
</tr>
<tr>
<td>%</td>
<td>Percentage</td>
</tr>
<tr>
<td>$1,25(OH)_2D_3$</td>
<td>1,25-dihydroxy vitamin D</td>
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INTRODUCTION

Even though calcium is one of the most abundant substances in the body, the plasma concentration of ionized calcium is only about 1.1 to 1.5 mmol/L. The total body calcium ranges from 1.0 to 1.5 kg (or about 1.5% of the total body weight), of which 99% is stored in the bones. Of the calcium in the plasma, 40% is bound to proteins (80–90% of that to albumin), 14% is complexed, and 46% is ionized. The latter 2 fractions are dialyzable. A balanced diet provides about 800–1200 mg of calcium per day, of which varying amounts are absorbed by the intestines (Popovtzer, 2003).

In dialysis clinics in the United States, the concentration of calcium in the dialysate is probably the most varied of all the electrolytes. The most common concentrations used today are 1.25, 1.5, and 1.75 mmol/L (i.e., 2.5, 3.0, and 3.5 mEq/L; or 5.0, 6.0, and 7.0 mg/ dL) (Sam et al, 2006).

The choice of dialysate calcium concentration is able to influence many of the most important factors in the successful management of chronic HD patients (Christopher, 2008).

Concentrations in the dialysate can be customized depending on the current and targeted serum Ca levels as well as the desire to maintain hemodynamic stability during dialysis (Palmer, 2001).

Long-term use of dialysate calcium with 1.25mmol/L would be associated with relatively lower serum calcium concentrations, which
would lead to more rapid elevation of iPTH and progression of secondary hyperparathyroidism (Hwang et al., 2008).

In haemodialysis patients with secondary hyperparathyroidism, a dialysate calcium concentration of 1.75 mmol/L results in better control of parathyroid overfunction and high turnover bone disease than with lower dialysate calcium concentrations (Molina et al., 2008).

Excessive lowering of serum calcium during the haemodialysis session by a low dialysate calcium concentration may be associated with more frequent episodes of hypotension and cardiac rhythm disturbances. Probably, the most life-threatening episodes are ventricular arrhythmias in association with concomitant hypokalaemia (Severi et al., 2008).

Cardiac arrhythmias are also more likely to occur in HD patients with lower dialysate Ca associated with the potential for worsening of QT prolongation (Nappi et al., 2000).
AIM OF THE WORK

The aim of this work is to investigate the relative role of Different Dialysate Calcium Concentrations on Parathyroid Hormone Levels and Cardiovascular stability in ESRD patients on regular hemodialysis.
CHAPTER I

Cardiovascular Disease in ESRD

Introduction:

Cardiac disease is the major cause of death, accounting for 41 percent of all-cause mortality in patients receiving hemodialysis (Lafrance et al., 2006).

Cardiac diseases are associated independently with a decrease in kidney function and progression of existing kidney diseases (Elsayed et al., 2007). In both the acute setting and more long-term phase, even small decreases in GFR are associated with adverse outcome (Coca et al., 2007).

Persons with CKD are predisposed to three types of CVD, atherosclerosis, arteriosclerosis, and cardiomyopathy when compared with age and gender matched persons with normal kidney function (Wali et al., 2005). In the past cardiovascular death was mainly viewed as the result of accelerated coronary heart disease (CHD). Although CHD is undoubtedly more frequent than in the background population, the importance of the two other, largely unresolved cardiovascular problems, Sudden death and cardiomyopathy (Remppis and Ritz., 2008).
Table (1): Risk Factors for Cardiovascular Disease in Kidney Disease

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<tr>
<th>Traditional Risk Factors</th>
<th>Nontraditional Risk Factors</th>
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<tr>
<td>• Age</td>
<td>• Kidney function decline</td>
</tr>
<tr>
<td>• Male sex</td>
<td>• Albuminuria</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Inflammation and oxidative stress</td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Disorders of mineral metabolism</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
<td>• Hyperphosphatemia</td>
</tr>
<tr>
<td>• Family history</td>
<td>• Changes in vitamin D metabolism</td>
</tr>
<tr>
<td>• Obesity</td>
<td>• Secondary hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>• Elevated FGF-23 levels (fibroblast growth factor 23)</td>
</tr>
<tr>
<td></td>
<td>• Activation of the sympathetic nervous system</td>
</tr>
</tbody>
</table>

**Uremic cardiomyopathy**

In chronic uremia, cardiomyopathy may manifest as concentric LVH, or left ventricular dilatation, and may result in diastolic or systolic dysfunction. These disorders are associated with the subsequent development of cardiac failure and with death (*Parfrey and Foley, 2005*).

**Concentric LVH**

Left ventricular hypertrophy (LVH) is a common finding in mild renal disease and end-stage renal disease, with some claiming an incidence of nearly 75 to 80 percent in dialysis patients (*Stewart et al., 2005*).

Left ventricular enlargement is very common at the starting of dialysis therapy, and highly predictive of future cardiac morbidity. It is
not known whether cardiac size increases further while on dialysis therapy and whether potentially reversible risk factors for later progression can be identified (Aoki et al., 2005).

**Myocardial fibrosis**

Myocardial fibrosis is not an obligatory consequence of hemodynamic stress and is more marked in pressure overload than in volume overload. The causes of myocardial fibrosis are multifactorial and include ischemia, and effects of hormones such as catecholamines, angiotensin II and aldosterone. Other studies have demonstrated that parathyroid hormone is a permissive factor in the genesis of cardiac interstitial fibrosis (London, 2002).

**Systolic dysfunction**

Decreased systolic function is observed frequently in patients with cardiac diseases preexisting before ESRD therapy or in patients with sustained and marked hemodynamic overload. Diminished myocardial contractility may be a result of overload cardiomyopathy (Parfrey and Foley, 2005).

**Diastolic dysfunction**

Diastolic filling is frequently altered in dialysis patients. The abnormal ventricular filling in ESRD results from increased LV stiffness caused by intramyocardial fibrosis and delayed relaxation. It is highly likely that patients with concentric LVH or LV dilatation have diastolic dysfunction, which predisposes to the development of heart failure (Parfrey and Foley, 2005).
Rhythm disturbance

Hemodialysis patients have a rate of arrhythmias that is 40 times greater than the general population, but the causes and types of fatal arrhythmias are still unclear. Dialysis increases the arrhythmogenic activity with respect to the inter-dialysis period to a great extent (Al-Khatib et al., 2007).

Abnormalities on resting electrocardiography are common in dialysis patients. Among patients who were enrolled in the 4D study (n = 1253), 11% had a rhythm other than sinus; three of four patients with an alternative rhythm had atrial fibrillation (Krane et al., 2009).

Most clinicians have been reluctant to administer prophylactic anticoagulation therapy for chronic AF in dialysis patients. Furthermore, the benefits versus risks from anticoagulation have not been accurately determined in these patients (Genovesi et al., 2009).

Dispersion of the QT interval has emerged as an important predictor of ventricular arrhythmia. The QT dispersion is simply the difference between the shortest and longest QT interval on a standard surface. This is a non invasive measurement of myocardial repolarization in homogeneity and hence predisposition to re-entry arrhythmias. A QT dispersion above 80 ms reflects a loss of synchronization in the repolarization process. The QT interval is partially influenced by the concentration of the dialyzable cations calcium, magnesium and potassium and may also be influenced by cardiac filling pressures (Fukuta et al., 2003).
To prevent hemodialysis-related myocardial arrhythmias, prolonged dialysis sessions with low ultrafiltration rates, careful titration of target weight and administration of oxygen during dialysis are recommended. Additionally, beta blockers seem to be an important therapeutic option in high risk patients (Fukuta H et al., 2003).

Hemodialysis patients administered on digitalis therapy have increased risk of arrhythmia. Also duration of hemodialysis, and acetate containing dialysate have close relation with occurrence of arrhythmias among hemodialysis patients. A high calcium phosphate product predialysis may be correlated with increased incidence of ventricular arrhythmias (Antonio et al., 2008).

Atherosclerotic disease

Because of the high prevalence of hypertension, LVH, diabetes, and lipid abnormalities in dialysis patients, it has been suggested that these patients have an accelerated rate of coronary atherogenesis. Atherosclerotic disease in CKD and in dialysis patients is somewhat different from that in the general population with atherosclerosis, as this atherosclerotic burden is further complicated by an increased frequency of calcific lesions, an increase in medial thickness and calcification involving medium to large sized vessels (Wali et al., 2005).

Multiple factors contribute to the vascular pathology of chronic uremia, including injury to the vessel wall, prothrombotic factors, lipoprotein interactions, proliferation of smooth muscle, hyperhomocysteinemia, increased oxidant stress, and diminished antioxidant levels (Wali et al., 2005).
**Congestive heart failure**

Not surprisingly, the presence of heart failure independently predicts early mortality in end-stage renal disease as it does in nonuremic patients (Postorino et al., 2007).

Congestive heart failure (CHF) may result from systolic failure, usually caused by dilated cardiomyopathy, or from diastolic dysfunction, usually caused by LVH. In fact diastolic dysfunction is almost as frequent cause of recurrent or persistent CHF in dialysis patients as is dilated cardiomyopathy (Aoki et al., 2005).

Among patients with diastolic dysfunction, CHF results from impaired ventricular relaxation, which leads to an exaggerated increase in LV end-diastolic pressure for a given increase in LV end diastolic volume. As a result, a relatively small excess of salt and water intake leads rapidly to a large increase LV end diastolic pressure, culminating in the pulmonary edema (Parfrey and Foley, 2005).

**Ischemic heart disease**

Evaluation for coronary artery disease should be performed in dialysis patients with symptoms and/or signs of coronary artery disease, a change in symptoms and signs, including recurrent hypotension, heart failure that is unresponsive to changes in dry weight, and intradialytic hypotension that prevents attaining dry weight (Gill JS et al., 2005).

The K/DOQI guidelines recommend that, at initiation of dialysis, all patients should undergo baseline echocardiography and electrocardiography (K/DOQI, 2005).