PREVALENCE OF HYPERCALCEMIA AND ITS POSSIBLE ASSOCIATIONS IN CHRONIC HEMODIALYSIS PATIENTS AT AIN SHAMS UNIVERSITY HOSPITALS

Thesis

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By

Ahmad Nasr El-ghitany

M.B..B.Ch..

Ain Shams University

Supervised by

Prof. Dr. Howaida Abdel-hamid El-Shinawy

Professor of Internal Medicine and Nephrology Faculty of Medicine, Ain Shams University

Dr. Essam Nour El-Din

Lecturer of Internal Medicine and Nephrology Faculty of Medicine, Ain Shams University

Faculty of medicine
Ain Shams University
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Protocol

Introduction

Abnormal mineral metabolism in patients with end stage renal disease ESRD is associated with bone and cardiovascular disease. Serum measurements of calcium, phosphorus, and parathyroid hormone (PTH) is associated directly with bone disease, cardiovascular outcomes, and mortality.(1)

Secondary hyperparathyroidism is common in patients with chronic kidney disease, affecting most of those who are receiving hemodialysis.(2)

Bone disease is the most widely recognized consequence of secondary hyperparathyroidism. Several reports indicate, however, that alterations in calcium and phosphorus metabolism, as a result of either secondary hyperparathyroidism or the therapeutic measures used to manage it, contribute to soft-tissue and vascular calcification, cardiovascular disease, and the risk of death.(3,4)

Episodes of hypercalcemia and hyperphosphatemia are often aggravated by the use of large doses of calcium as a phosphate-binding agent, particularly in combination with vitamin D sterols, which increase the absorption of calcium and phosphorus.(5)

Vascular calcification, a widely recognized and common complication of chronic kidney disease (CKD), increases the risk for cardiovascular morbidity and mortality. Although the causes of vascular calcification in CKD remain to be elucidated, associated risk factors include age, hypertension, time on dialysis, and abnormalities in calcium

(Ca) and phosphorus (P) metabolism, resulting in a raised serum Ca-P product (Ca x P).(6)

Anaemia accompanies abnormal mineral metabolism during progressive renal failure, largely due to erythropoietin deficiency, marrow fibrosis, blood loss, malnutrition and shortened red blood cell survival. Several investigators have suggested a link between mineral metabolism and anaemia. Hyperparathyroidism is usually listed as a contributor to renal anaemia and as a possible reason for impaired response to recombinant human erythropoietin (rHuEpo) in patients with renal disease. Possible pathogenic links between anaemia and iPTH include reduced erythropoiesis due to calcitriol deficiency, direct or indirect effects of iPTH on erythropoietin release and shortened red blood cell survival.(7)

Left ventricular hypertrophy is very common in both predialysis and postdialysis patients. It occurs secondery to pressure overload from hypertension, stiffened blood vessels, or aortic valve stenosis. Disordered mineral metabolism has also been associated with left ventricular hypertrophy with identified risk factors including elevated calcium phosphate product, and elevated serum parathyroid hormone. Left ventricular hypertrophy is seen most frequently in ESRD and, together with increased cardiomyocyte Ca⁺⁺ content, contributes to systolic and diastolic dysfunction, myocardial ischemia, and increased cardiac mortality in ESRD.(8)

The mechanisms by which hyperparathyroidism could favor LVH are theoretically several and include direct trophic effects on myocardial myocytes and on interstitial fibroblasts and indirect effects such as an increase in blood pressure via hypercalcemia, anemia, and large and small vessel changes.(9)

Aim of the work:

The aim of this thesis is to define the prevalence of hypercalcemia and its possible associations in hemodialysis patients in Ain shams university hospitals.

Patients & methods:

Our study will include all patients receving regular hemodialysis in Ain shams university hospital & Ain shams specialized hospital

All patients will be subjected to the following:

Full history and clinical examination stressing on:

- Hemodialysis duration.
- Etiology of chronic renal failure.
- Drug history.

Laboratory investigations including:

- Serum creatinine.
- Blood urea nitrogen.
- Calcium.
- Albumin.
- Phosphrous.
- Alkaline phosphatase.
- Parathyroid hormone

Exclusion criteria:

Patients on hemodialysis less than three months duration.

References

- 1. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42[Suppl 4]: S1–S201.
- 2. Owda A. Elhwairis H, Narra S, Towery H, Osama S. Secondary hyperparathyroidism in chronic hemodialysis patients: prevalence and race. Ren Fail 2003; 25:595-602.
- 3. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in hemodialsis patients: a lnk between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002; 39:695-701.
- 4. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO₄, Ca x PO₄ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-2138.
- 5. Johnson CA, McCarthy J, Bailie GR, Deane J, Smith S. Analysis of renal bone disease treatment in dialysis patients. Am J Kidney Dis 2002; 39:1270-1277.
- 6. Giachelli CM: Vascular calcification mechanisms. J Am Soc Nephrol 2004; 15: 2959 –2964.
- 7. Drücke T. Hyporesponsiveness to recombinant human erythropoietin. Nephrol Dial Transplant 2001; 16 [Suppl 7]: 25–28.
- 8. Duprez D, Bauwens F, De Buyzere M, De Backer T, Kaufman J-M, Van Hoecke J, Vermuelen A & Clement DL. Relationship between parathyroid hormone and left ventricular mass in moderate essential hypertension. J Hypertens 1991; 9 Suppl 6: S116–S117.
- 9. Rostand SG & Rutsky EA. Ischemic heart disease in chronic renal failure: Demography, epidemiology, and pathogenesis,. In Cardiac Dysfunction in Chronic

Uremia 1992; edited by Parfrey PS, Harnett JD Norwell, Kluwer Academic Publishers p 53.

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List of Contents

List of Abbreviation	ii
List of Figures	iii
List of Tables	V
Protocol	1
Review of literature	4
Patients and methods	59
Results	64
Discussion	78
Summary and recommendations	89
References	93
Arabic Summary	

LIST OF ABBREVIATIONS

1,25(OH)2D3	1,25-dihydroxy calcitriol
Ca	Calcium
$Ca \times P$	calcium-phosphorus product
CaR	calcium sensing receptor
CKD	Chronic kidney disease
CRF	chronic renal failure
CRI	Chronic renal insufficiency
CVD	Cardiovascular disease
CUA	Calcific uremic arteriolopathy
DOPPS	Dialysis Outcomes and Practice Pattern Study
ESRD	End stage renal disease
FDA	Food and drug administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDF	haemodiafiltration
iPTH	Intact parathyroid hormone
K/DOQI	Kidney Disease Outcomes and Quality
	Initiative
LDL	Low density lipoproteins
LHD	long haemodialysis
NDHD	nocturnal daily haemodialysis
NKF	National Kidney Foundation
nPCR	Normalized protein catabolic rate
P	Phosphorous
QB	Pump speed
rHuEpo	Recombinant human erythropoietin
RXR	retinoid X receptor
SDHD	short daily haemodialysis
SHPT	Secondary hyperparathyroidism
VDR	vitamin D receptor
VDRE	vitamin D response element

LIST OF FIGURES

	<u> Libi di i icones</u>	
Figure no.	Title	Page
Figure (1)	A comparison of serum phosphate relative reduction	15
	kinetics during three sequential dialysis prescriptions.	
Figure (2)	Schematic illustrating four, non-mutually exclusive	43
	theories for vascular calcification.	
Figure (3)	Proposed model for the effects of elevated Ca and P	46
	on vascular smooth muscle cell (SMC) matrix	
	mineralization.	
Figure (4)	Frequency distribution of patients achieving K/DOQI	69
	target levels for calcium, phosphorus, Ca×P, and	
	iPTH.	
Figure (5)	Comparison between proportion of patients achieving	79
	K/DOQI target for calcium (8.4-9.5 mg/dl) in	
	Europe, U.S., Japan and our study.	
Figure (6)	Comparison between proportion of patients achieving	82
	K/DOQI target for phosphorus (3.5-5.5 mg/dl) in	
	Europe, U.S., Japan and our study.	
Figure (7)	Comparison between proportion of patients achieving	84
	K/DOQI target for Ca×P product (< 55 mg2/dl2) in	
	Europe, U.S., Japan and our study.	
Figure (8)	Comparison between proportion of patients achieving	86
	K/DOQI target for iPTH (150- 300 pg/ml) in Europe,	
	U.S., Japan and our study.	

LIST OF TABLES

<u>LIST OF TABLES</u>			
Table no	Title	Page	
Table (1)	NKF-K/DOQI treatment targets for the management of iPTH, calcium, phosphorus and Ca×P in patients requiring dialysis	7	
Table (2)	A strategy to control hyperphosphataemia	16	
Table (3)	Algorithms for prophylaxis of secondary hyperparathyroidism	25	
Table (4)	Treatment of advanced hyperparathyroidism	26	
Table (5)	Causes of hypercalcaemia in patients with chronic renal failure	31	
Table(6)	Clinical Manifestations of Hypercalcemia	40	
Table (7)	Causes of adynamic renal osteodystrophy	55	
Table (8)	Distribution of gender among studied patients	64	
Table (9)	Age descriptive data in the studied patients	64	
Table (10)	Dialysis data including duration of dialysis, dry weight, systolic and diastolic blood pressure in studied patients.	64	
Table (11)	Aetiology of chronic renal failure in studied patients.	65	
Table (12)	Prevalence of HCV, HBV and HIV infection in studied patients.	65	
Table (13)	Prevalence of cerebrovascular disease, ischemic heart disease, peripheral vascular disease, hypertension and itching in studied patients.	66	
Table (14)	Laboratory data including serum calcium, phosphorus, calcium X phosphorus product, PTH, albumin, alkaline phosphatase, BUN, creatinine and haemoglobin in studied patients.	66	
Table (15)	Frequency distribution of patients using aluminium based P binders, calcium based P binders and alfacalcidol.	70	
Table (16)	Dose of elemental calcium and alfacalcidol in studied patients.	70	