FEATURES OF PHOSPHOCALCIC METABOLISM DISORDERS IN PATIENTS UNDERGOING DIALYSIS AT A HEMODIALYSIS CENTER LOCATED IN WEST-ROMANIA.

SUMMARY:
Phosphocalcic metabolism disorders remain a topical issue for patients undergoing dialysis. For them a special problem is represented by extraskeletal calcifications. Vascular and valvular calcifications represent a risk for the occurrence of cardiovascular events in dialysis patients. Treatment of hypocalcemia and hyperphosphoremia may be accompanied as well by the increased risk for vascular calcifications. Vascular calcifications are detected by noninvasive imaging methods.

Our goal is to analyze the particularities in these variations for patients undergoing haemodialysis in The Haemodialysis department of SCJUTimisoara during 2009.

Material and Method: We have evaluated 30 patients with chronic renal failure treated by the means of hemodialysis in The Hemodialysis Center of SCJUT, which were hospitalized during 2009. Of the 30 patients included in the study, 11 (37%) were women and 19 (63%) were men.

Results: The study group mean age was 57.6 ± 10.85 years, gender distribution was 11 (37%) women and 19 (63%) men. The average duration of hemodialysis was 11 ± 3.17 years. (Minimum 6 years and maximum 19 years). The study group had calcifications of the MV 17 (57%) patients, calcifications of AV 12 (40%) and pericardial calcifications in 9 (30%) patients. X-Ray examination of the thorax detected aortic button calcifications in 12 (40%) patients. Peripheral angiography was done in 7 (23%) patients that have shown plaque buildup in the aorta, femoral artery, ILAC, popliteal, tibial. Radiological examinations have shown: — the ankle: diffuse bone demineralization in 27 (90%) patients; mediocalcoza 7 (23%) patients, areas of osteolysis in 5 (17%) patients, vascular calcifications in 5 (17%) bilateral soft tissue calcifications in 2 (7%) patients. — the hands: demineralization in 28 (93%) patients, geodes in 17 (57%) patients, areas of osteolysis in two (7%) patients; mediocalcoza 10 (33 %) patients, collapse of joint space in three (10%) patients.

Our study highlights the fact that extraskeletal calcifications are present in over 50% of patients undergoing dialysis, both at vascular and valvular level. It also allows assessment of treatment of secondary hyperparathyroidism, using those therapies to promote regression of extraskeletal calcifications in order to prevent cardiovascular events in dialysis patients.

Key Words: hyperparathyroidism, extraskeletal calcifications, dialysis patients

PARTICULARITĂȚI ALE TULBURĂRILOR METABOLISMULUI FOSFOCALCIC LA PACIENTII DIALIZAȚI ÎNTR-UN CENTRU DE HEMODIALIZĂ DIN VESTUL ȚĂRII

Rezumat:
Tulburările metabolismului fosfocalcic ramane o problema de actualitate și la pacientul dializat. La pacientul dializat o problema deosebită o reprezinta calcificările extrascheletale. Calcificările vasculare și valvulare reprezintă un risc pentru aparitia evenimentelor cardiovasculare la pacientul dializat. Tratamentul hipocalcemiei si hiperfosforemiiei se poate insiti de asemenea de creșterea riscului pentru accentuarea calcificărilor vasculare. Calcificările vasculare sunt decelate prin metode imagistice neinvasive. Ne-am propus sa analizam particularitatile acestor modificari la pacientii dializati, in sectia de Hemodializa a SCJUTimisoara in cursul anului 2009.
Phosphocalcic metabolism in dialysis patients was studied both in terms of cardiovascular risk and in the intimate mechanisms of genetic alterations responsible for these changes. Risk factors for vascular calcifications in patients undergoing dialysis are represented by age, sex, duration of dialysis, inflammatory status, abnormal phosphocalcic metabolism and diabetes [1]. In patients with end stage renal disease life expectancy is significantly lower, cardiovascular disease being the cause of more than half of all deaths [2;3]. The risk of death increases by 500 to 1000 times in dialysis patients. Traditional cardiovascular risk factors as hypertension, left ventricular hypertrophy, dyslipidemia and hiperhomocistinemia only partly explain the accelerated mortality in dialysis patients. Probably, there are additional risk factors that contribute to the development of accelerated atherosclerosis and uremic arteriopathy [4; 5]. In patients with chronic kidney disease, vascular changes consist of mediae and intimae calcifications associated with vascular atherosclerosis. The degree of vascular stiffness and vascular calcifications represent prognostic markers of cardiovascular risk in dialysis patients. [6;7] Although the vascular calcification process is not fully elucidated, it is not just a passive deposition of calcium phosphate crystals, but it is an active, complex, process involving a specific cellular protein synthesis. [1] A number of proteins have the ability to induce vascular and extraskeletal calcification. In recent years, studies have been focused towards investigating the role of various proteins’ genetic polymorphism as risk factors in patients undergoing dialysis. [8;9] A role in the mortality in the induction process of extraskeletal calcification and connective tissue remodeling in uremic patients is played by the metalloproteinase of the matrix. [10] Recent data have shown the association of metalloproteinase MMP1 and MMP3 polymorphism with risk factors for mortality in the case of hemodialysis patients. [11] The metalloproteinase are a family of enzymes involved in extracellular matrix biology and in atherosclerosis. Metalloproteinase MMP1 and MMP3 are involved in the expansion and buildup of plaque instability. [12;13] Accelerated atherosclerosis and cardiovascular disease is associated with MMP3 gene polymorphism. The proteolytic activity of metalloproteinase MMP3 has effect on some proteins of the extracellular matrix and may activate other metalloproteinase. [14; 15] Metalloproteinase MMP3 also has an important role in cardiac and vascular matrix remodeling. [15] Vascular calcification increases the risk of cardiovascular events. [1] Metalloproteinase MMP3 expression coexists with calcium deposits in atherosclerotic lesions. [16] The constituents of atherosclerotic lesions are matrix
proteins: collagen, proteoglycans, elastin, smooth muscle cells, macrophages and lipids. [17] Also involved are the changes of the genetic polymorphism of fetuin-A (alfa2-HS glycoprotein - AHSG) and matrix GLA protein(GP). [18;19] Hemodialysis patients show a chronic inflammatory status represented by the low level of fetuine A. Fetuina A is a multifunctional protein synthesized by the liver that belongs to the super-family of cistatine. It is a glycoprotein with molecular weight of 62kD which prevents ectopic calcifications. [20] Its serum level is decreased in patients with calciphylaxy[21].

Chronic inflammation is also associated with an increased risk of cardiovascular disease in dialysis patients. Ketteler [22] showed that in dialysis patients fetuin A is an independent predictor of cardiovascular events. In dialysis patients there is a relationship between serum levels of fetuin A and genetic polymorphism. [23]

Matrix GLA protein, is a vitamin K dependent protein, with a molecular weight of 10kD and is present in the cartilage, bone and arterial wall matrix, which inhibits calcium phosphate deposit. MGP expression is strong in the plaque buildup. [24] MGP is a negative prognostic factor in cardiovascular patients undergoing hemodialysis.[25]

Since literature data on phosphocalcic metabolism changes refers especially to patients with chronic renal failure in the predialytic stage, we aimed to analyze the features of these changes in patients undergoing dialysis in a hemodialysis center located in the west of Romania.

MATERIAL AND METHOD

We have evaluated 30 patients with CRF undergoing hemodialysis in the Hemodialysis Center of SCJU Timisoara, in 2009. All patients had been evaluated biologically and by means of non-invasive paraclinical methods. All patients were investigated biologically, the following parameters being determined: serum creatinine (CHOD-PAP method), triglycerides (GPO-PAP method), cholesterol, C-reactive protein (immunoturbidimetric method Dade-Behring), hemoglobin (Hb spectrophotometric method / LYSE WIC with K+ and quaternary ammonium salt), PTH: immunochemical method with detection by electrochemiluminiscence (ECILA), serum calcium through complexometric titration, serum phosphorus and alkaline phosphatase spectrophotometric method, glomerular filtration rate (GFR) - modification of Diet in Renal Disease MDRD4 - Study equation), glycinemia (glucozoxidasis method). According to laboratory techniques the values that were considered pathological were: glycemia > 120 mg / dl, serum cholesterol > 220 mg / dl, triglycerides > 200 mg / dl, C-reactive protein > 3 mg / L, hemoglobin < 12 grams / dl in men and < 11g/dl in women, serum calcium < 8.4mg% phosforemia > 4.7 mg% phosphocalcic product > 55mg%, alkaline phosphatase > 150U per liter, serum PTH > 65 pg / ml.

In terms of paraclinical investigations we performed: radiological examinations (chest, hands and legs X-Ray, cardiac ECO, CT (angiography and peripheral), parathyroid scintigraphy.

Bone lesion status was examined by measuring bone mineral density at the level of the lumbar spine and hip by the absorptionometric dual X-ray method using clinical classification of osteoporosis set by WHO and adopted in 1998 by the International Osteoporosis Foundation which takes into account bone loss and partially the risk of fracture, using T-score (normal T score > -1, osteopenia T-score between -1 and -2.5, osteoporosis T-score <= -2.5).

Exploration of extraskeletal calcifications was achieved by performing chest X-Ray for evidence of thoracic aortic calcifications and transthoracic echocardiography to detect pericardial and valvular calcifications. Patients were subjected to multi slice CT for the detection of calcifications located on the peripheral vessels.

RESULTS

The study group mean age was 57.6 ± 10.85 years, gender distribution was 11 (37%) women and 19 (63%) men. The average duration of hemodialysis was 11 ± 3.17 years. (Minimum 6 years and maximum 19 years).

From the biologically point of view the study group produced the following results: The average value of calcium was 8.65 ± 0.74 mg / dl (minimum value = 7.4, maximum value = 10.2).

Mean phosphorus value was 6.53 ± 1.42 mg / dL (minimum value= 5.2 , maximum value = 8.2). The mean calcium-phosphorus product was 57.02 ± 15.66 (minimum value = 55, maximum value = 76).

The study group’s mean PTH was 1113 ± 477.1 pg / ml (minimum value = 300, maximum value=2345).

Alkaline phosphatase had an average of 299.9 ± 342.07u / l.

Inflammatory status was assessed by determining the CRP, which showed an average of 18.06 ± 20.96mg/L.

Pruritus was recorded in a total of 10 (33%) patients.
Bone pain was recorded in 12 (40%) patients and 4 (13) had amputations.

CT scan showed that 25% of the study group had calcified abdominal aorta without stenosis, bilateral femoral artery calcified, stenosed in percentage of 50-70%, parietal plate calcified popliteal artery, tibial artery calcified bilaterally, apparently permeable bilaterally (difficult to assess due to calcification).

Echocardiographic parameters revealed calcifications both on the valves and the pericardium. The study group had calcifications of the MV 17 (57%) patients, calcifications of AV 12 (40%) and pericardial calcifications in 9 (30%) patients.

Radiological examinations have shown: — the ankle: diffuse bone demineralization in 27 (90%) patients; mediocalcozis 7 (23%) patients, areas of osteolysis in 5 (17%) patients, vascular calcifications in 5 (17%) bilateral soft tissue calcifications in 2 (7%) patients. — the hands: demineralization in 28 (93%) patients, geodes in 17 (57%) patients, areas of osteolysis in two (7%) patients; mediocalcoza 10 (33%) patients, collapse of joint space in three (10%) patients.

X-Ray examination of the thorax revealed 12 (40%) patients had aortic button calcifications. (Fig.1)

Peripheral angiography was performed in 7(23%) patients that have shown calcifications the aorta, femoral artery, iliac, popliteal, tibial.

DEXA showed osteoporosis at the lumbar level in 17 (57%) patients and osteopenia in 12 (40%) patients, while at the hip level osteoporosis in 11 (37%) patients and osteopenia in 18 (60%) patients.

Examination of parathyroid scintigraphy with Tc-99m MIBI “dual-phase” done to all those 30 patients showed 14 (67%) with parathyroid hyperplasia.

The patients that followed a treatment with calcium acetate renagel represent a total of 9 (30%), renagel and Zemplar 12 (40%), renagel a total of 3 (10%), Calcium 2 (7%) patients, calcium acetate and Zemplar a total of 4 (13%) patients.

DISCUSSIONS

Our study revealed the presence of phosphocalcic metabolism changes in all patients.

Mean serum calcium in patients included in the study was 8.65 ± 0.74 mg/dL.

The most common cause of cardiovascular disease is represented by this excess of vascular calcifications. The extensive coronary artery calcifications form was observed in young dialysis patients [26; 27; 28;29].

Several factors have been incriminated: vitamin D therapy, age, duration of dialysis. Calcium is stored in both mediae and in intimae of blood vessels. Most authors argue that calcium storage in the vessels of dialysis patients is associated with vascular stiffness. In general, intimae and mediae calcifications are located at the level of the coronary, aorta and iliac and femoral arteries.
Simple or flat radiography may reveal extraskeletal calcifications, especially vascular. Simple radiography has the advantage that it can be easily interpreted and used to detect patients at risk of developing cardiovascular events.

It is a noninvasive and insensitive method which does not quantify vascular calcification.

In our study, simple chest radiography showed calcifications of the aortic knob to 12 (40%) patients. Flat X-Ray can diagnose vascular calcifications and based on the X-ray pattern can differentiate the calcification of the intima from the calcification of the mediae [30]. Mediae calcification presents as a linear or continuous double line, and intima calcification is in the form of irregular deposits. Hypercalcemia and hyperphosphatemia are associated with both types of calcifications.

Abdominal aortic calcifications can be assessed by Kaupilla score. Bellasi has shown that dialysis patients Kaupilla score (abdominal aortic calcification) correlates with Agatston score (coronary artery calcification) [31;32]

Simple X-Ray centered at the pelvis evaluated femoral and iliac arteries (ileo-femoral score) and centered at the the hands evaluated radial and digital arteries (hand score). Each section is evaluated by presence or absence of calcification. It includes both the mediae and intimae calcifications.[33]

Peripheral angiography was performed in 7(23%) patients that have shown calcifications the aorta, femoral artery, ilac, popliteal, tibial.

Valvular calcifications were highlighted by echocardiography at the aortic valve in 12 (40%) patients and the mitral valve in 17 (57%) patients. Pericardial calcifications were highlighted in 9 (30%) patients. It is demonstrated that this mitral or aortic valve calcifications assessed ecocardiograficly is associated with a low survival rate.[34]

Vascular calcification in dialysis patients is a predictor of valvular calcifications. Patients with vascular calcifications have an increased risk to present valvular calcifications, which suggest that calcification appearing in patients’ records, that are undergoing dialysis is a systemic disorder.

Literature studies have shown that these cardiac calcifications (valvular, myocardial and pericardial) are significantly more common in dialysis patients compared with the general population [35].

Coronary artery calcifications in the general population are present only in the presence of atherosclerosis. Recent studies showed that calcifications of the coronary artery in dialysis patients are: premature, vast and rapidly progressive. [36;37;38]

Mineral metabolism changes present in these patients may contribute to increased incidence of cardiovascular events [39; 40;41;42]. Hyperphosphatemia, hypercalcaemia and secondary hyperparathyroidism and treatment used to control these disorders are involved in the development of vascular and visceral calcifications [43;44].

Progressive calcification of aorta and coronary arteries was found in patients treated with calcium salts but not in those treated with sevelamer. Lack of association between calcium and phosphate levels and the progression of vascular calcifications reflects a decrease in substrate or alteration in the bone dynamics with a predilection towards mineralization rather than towards visceral calcification.

The severity of vascular calcifications is in correlation with hypercalcemia and hiperphosherea [45; 46]. The relationship between the phosphocalcic metabolism disorders and vascular calcification is not completely understood.

Recent studies on cell cultures showed that exposure of smooth muscle cells in the aortic mediae to a higher concentration of phosphate leads to an increased, dose-dependent, calcium deposits [47]. Phosphate-induced calcification is related to the expression of osteocalcin, an osteogenic marker. [48]

Epidemiological studies have shown that the severity and progression of the vascular calcifications in dialysis patients is dependent on the amount of calcium salts administered for the treatment of hyperphosphatemia [49; 50; 51]

Abuse of vitamin D analogues for lowering PTH is associated with the establishment of severe extraskeletal calcifications [52]. The use of new vitamin D derivatives, Paricalcitol, allows control of PTH synthesis and secretion, but with little hypophosphataemic and hypercalcaemic effect. [53]

Phosphate – binders which contain calcium phosphate worsen vascular calcifications by favoring the formation of pathological - bone. The administration of sevelamer is accompanied by minor vascular calcifications [54 ]. Some studies recommend the administration of 1.5g/day acetate or calcium carbonate [55]. Because there was a correlation between average dose of calcium salts and progression of calcifications it was demonstrated the need to administer small doses of calcium salts, particularly in patients treated with vitamin D.

Calcimimetics (calcium receptor activators), are effective in the treatment of vascular calcifications and
prevent secondary hyperparathyroidism, parathyroid hyperplasia and vitamin D receptor expression in parathyroid glands [56;57]. Calcimimetics lower phosphoremia and lower serum calcium thus preventing precipitation of mineral salts [57].

Calcimimetics promote the regression of vascular mineralization in uremic rats by the means of raising the values of urinary calcium and/or resorption of calcium deposits [58]. Prolonged treatment with cinacalcet for a period of one year on a patient suffering from calciphylaxis led to a decrease in ectopic calcifications [59].

Some studies have shown a correlation between the severity of vascular calcifications and increased levels of calcium and phosphorus.

Amputations occurred in 5 (17%) patients. A study on a group of dialysis patients showed a 6% prevalence of amputation in patients, with a mean survival after amputation of 2 to 3.4 years [60].

CONCLUSION

Our study highlights the fact that in dialysis patients, extraskeletal calcifications are present in over 50% of patients, both at vascular (23 patients - 77%) and valvular (21 patients - 70%) level. Also, the evaluation of the therapeutical methods allows the assessment of treatment in case of secondary hyperparathyroidism, using those therapies to promote the regression of extraskeletal calcifications, in order to prevent cardiovascular events in dialysis patients.

REFERENCES

References (Continued):


References (Continued)