SPECIFICITIES OF THE PHOSPHO-CALCIC METABOLISM IN PATIENTS WITH CRONIC RENAL DISEASE IN INITIATING THE ASSISTED SUBSTITUTION OF THE RENAL FUNCTION IN A HEMODIALISIS CENTER IN WESTERN ROMANIA

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SUMMARY: The chronic renal disease by slow progressive sitruction of the nefrons advances towards cronic renal failure. One of the manifestations of chronic renal failure are the perturbations of the phospho-calcic metabolism. These perturbations worsen with the progression of the alteration of the glomerular filtration rate. The complex perturbations of the phospho-calcic metabolism cause renal osteodystrophy. These perturbations are represented by hypocalcemia, hyperfosfatemia, and hypersecretion of PTH which become worse as glomerular filtration decreases. The chronic renal failure patients develop extra-skeletal calcifications both at the level of vessels and at that of soft tissues. We set to ourselves to analyze the specificities of these changes in patients with renal failure at the start of hemodialysis in a hemodialysis center in the western part of this country. MATERIAL AND METHOD: We assessed 30 stage V cronal renal disease patients with GFR below 10ml/min hospitalized for initiation of renal substitution therapy by hemodialysis in the Hemodialysis Department of the IUCCH during 2009. Of the 30 patients under study 12(40%) were women and 18(60%) were men. RESULTS OBTAINED: In the group under study, the age was 48.83±16.79 years (between 42 and 72 years). The etiology of chronic renal failure was represented by GNC -10 (33%) cases, polycystic kidney – 3 (10%) cases, PNC- 4 (13%) cases, nephroangiosclerosis 6 (20%) cases, diabetes – 6 (20%) cases and surgically acquired single kidney-1 (4%) case. Of the group studied, 24 (80%) patients were put into family doctor’s clinics and 21 patients underwent calcium and/or alph a D3 therapy. Of these, 19 cases underwent alpha D3 and calcium treatment and 2 cases underwent only calcium therapy. The average value of calcium was 8.58±0.94 mg/dl. It was found that 11(37%) patients, showed hypocalcaemia. The average value of phosphorus was 6.53±1.82 mg/dl. It was noticed that 26 (87%) patients showed hyperfosfatemia and 4 (13%) patients had normal values. The average value of the phosphocalcic product was 56±15.82 mg%. The average value of PTH was 351±228.76 pg/ml. Of the group under study, 10 (33%) cases showed osteoporosis and 10 (33%) cases had osteopenia in the lombar spine, and 7 (23%) showed osteoporosis in the hips. Radiologic examination revealed 6 (20%) cases of vascular calcification revealed by aortic button calcification, the rest showing normal parameters. Echocardiography was performed in 19 patients. It revealed a normal aspect of the valves and of the pericardium in 11 (58%) patients, thickened pericardium with calcifications in 1 (5%) patient, valvular calcifications in 2 (10%) patients, mitral ring calcification in 1 (5%) patient. Our study has revealed the fact that affection of the phosphocalcic metabolism is present in patients with renal failure in pre-dialytic stage. Knowledge of the changes that occur in the phosphocalcic metabolism in patients with renal failure in pre-dialytic stage is important for its correct treatment. Therefore, this study directs our attention towards the vascular and cardiac changes in these patients, offering us the possibility of a correct treatment of arteriosclerosis and of extraskeletal calcifications.

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The chronic renal disease by slow progressive sitution of the nefrons advances towards chronic renal failure. About 6-11% of individuals in the adult population hace cronic renal disease in various stages, and a number of them advance towards the end stage of renal failure [1].

One of the manifestations of chronic renal failure are the perturbations of the phospho-calcic metabolism. These perturbations worsen with the progression of the alteration of the glomerular filtration rate. The complex perturbations of the phospho-calcic metabolism cause renal osteodystrophy. These perturbations are represented by hypocalcemia, hyperphosphatemia, and hypersecretion of PTH which become worse as glomerular filtration decreases. The chronic renal failure patients develop extra-skeletal calcifications both at the level of vessels and at that of soft tissues. The presence of extra-bone calcifications increases the morbidity and the mortality rates in those patients [2]. Vascular calcification is polifactorial and incompletely understood. Until recently this process was considered a passive consequence of ageing.

Mineralization of the vascular wall is an active process, regulated at cellular level and is not exclusively determined by depositing of mineral salts at the level of soft tissues. [3]. Chronic inflammation and acidosis favour release of substances by endothelial cells that include the phenotipical transdifferentiation of flat muscular vascular cells into osteoblast-like cells [4, 5]. Some studies indicate that the pressure of osteoblastic cells in the vascular cell is the final result of phenotypic changes of flat vascular muscular cells.

Phosphorus is considered to be the most important factor in the pathogenesis of vascular calcifications.
Hyperphosphatemia and the increased phospho-calcic product play an important role in vascular calcification [6]. Hyperphosphoremia induces the precipitation of phosphocalcic cells under the form of apoptotic bodies or vesicles at the level of the extracellular matrix [7].

The role of phosphorus in vascular calcification is much more important than that of extra-cellular calcium [8]. Calcium plays a role in the development of the vascular calcifications by calcium depositing in the soft tissues or by activation of the receptors sensitive to calcium and of the calc channels at the level of flat vascular muscular cells. [9] Like phosphorus, calcium causes the transdifferentiation of flat muscular cells into osteogenic cells [10].

Osteo-immunohistochemical anomalies in the chronic renal disease occur early after diminution of the GFR below 90 ml/min and before seric changes of phosphorus, calcitriol and PTH [11, 12]. Uremic patients are subject to metabolic calcifications caused by imbalance of the mineral system associated with dissemination of ectopic calcifications [13, 14]. This predisposition appears if the phospho-calcic product is increased (Bloks). Ectopic calcifications cause particular clinical problems when they appear in the vessels of uremic patients and contribute to the morbidity and mortality associated with uremia. [15].

Back in 1979 Alfrey demonstrated that the arteries of chronic renal disease patients show more calcifications then the healthy persons of the same age [16].

**Aim:**

As data in the literature concering the changes in the phospho-calcic metabolism refers especially to the dialysed patients, we set to ourselves to analyse the specificities of these changes in patients with renal failure at the start of hemodialysis in a hemodialysis center in the western part of this country.

**MATERIAL AND METHOD**

We assessed 30 stage V chronic renal disease patients with GFR blow 10ml/min hospitalized for initiation of renal substitution therapy by hemodialysis in the Hemodialysis Department of the IUCCH during 2009. Of the 30 patients under study 12(40%) were women and 18(60%) were men.

All the patients were assessed biologically and paraclinically by non-invaze methods: Osteodensitometry, Thorax Rx and cardiac ECHO examination were performed, from the paraclinical point of view, and calcemia, phosphatemia, PTH and FA, phospho-calcic product, reactive C-protein and glomerular filtration rate analysis were performed from the biological point of view.

All the patients were investigated biologically, the following parameters being determined: seric creatinine (CHOD-PAP method), triglicerides (the GPO-PAP method) reactive C protein (the DADE-BEHRING immunoturbidimetric method), hemoglobin (Hb/WIC LYSE spectrofotometric Hb with K+ and ammonium quaternary salt) PTH, the immunochemical method with detection by electrochemiluminescence (ECLIJA), seric calcium by complexometric titration, seric phosphorus and alkaline phosphatase by the spectrophotometric method, glomerual filtration rate (GFR) (modification of Diet in Renal Disease MDRD4 –Study Equation), glicemia (the glucosoxidase method).

According to laboratory techniques the values beyond which the parameters studied were considered pathological were: glicemia > 120 mg/dl, seric cholesterol >220 mg/dl, triglycerides >200 mg/dl, reactive C protein >3 mg/l, hemoglobin < 12g/dl in men and <11g/dl in women, calcemia <8.4 mg%, phosphoremia >4.7 mg%, phosphocalcic product >55 mg%, alkaline phosphatase >150 U/L, seric PTH >65 pg/ml.

The status of bone lesions was analyzed by measuring bone mineral density at the level of the lombar spine and the hips by dual ray absorbtionmetry method using the clinical classification of osteoporosis established by W.H.O. , adopted in 1998 and by the international Osteoporosis Foundation, which takes into account the loss of bone mass and partially the fracture risk, using the T scoring system (normal score T>-1; osteopenia, score ranging between -1 and -2.5, osteoporosis score T<-2.5)

Exploration of exoscheletal calcifications consisted of thorax radiography for revealing calcifications of the thoracic aorta, and transthoracic echocardiography for detecting pericardic and valcular calcifications.

The patients did not undergo multiple slice CT for the detection of calcifications located at the level of peripheral vessels.

**RESULTS**

In the group under study, the age was 48.83±16.79 years (between 42 and 72 years). The distribution by sex being 12 (40%) women and 18 (60%) men.

The etiology of chronic renal failure was represented by GNC -10 (33%) cases, polycystic kidney – 3 (10%) cases, PNC- 4 (13%) cases, nephroangiosclerosis 6
(20%) cases, diabetes – 6 (20%) cases and surgically acquired single kidney-1 (4%) case.

Of the group studied, 24 (80%) patients were put into family doctor’s clinics and 21 patients underwent calcium and/or alpha D3 therapy. Of these, 19 cases underwent alpha D3 and calcium treatment and 2 cases underwent only calcium therapy.

From a biological point of view:
- The average value of calcium was 8.58±0.94 mg/dl. It was found that 11(37%) patients, 5 women and 6 men, showed hypocalcaemia (the normal value of calcium being 8.4 – 10.2 mg/dl). (Fig. 1)

- The average value of phosphorus was 6.53±1.82 mg/dl. It was noticed that 26 (87%) patients showed hyperphosphatemia and 4 (13%) patients had normal values. (Fig. 2)

- The average value of the phosphocalcic product was 56±15.82 mg%. In 14 (47%) patients its value was over 55mg%. (Graph No. 3)

- The average value of AF at the start was 129.53±77.07 U/L, being increased in 10 (33%) of the patients in the group studied.

- The average value of PTH was 351±228.76 pg/ml (N= 5-65 pg/ml). In 12 (40%) patients PTH was over 300 pg/ml, in 16 (53%) patients it was between 150 and 300 pg/ml and in 2 (7%) patients it was over 800pg/ml.

- The average value of CRP was 8.73±10.05mg/dl. In 24 (80%) patients we found values of CRP over 3mg/l.

- The average value of cholesterol was 124.93±48.32 mg%. We found: dyslipidemia in 11 (37%) patients, hypercholesterolemia 9 (30%) patients and hypertriglyceridemia in 8 (27%) patients.

We observed the existence of a reverse correlation between clacemia and phosphatemia, r=-0.085, and between calcemia and PTH r=-0.136. We found a direct correlation between calcemia and the phosphocalcic product r=0.295.

Of the group under study, 10 (33%) cases showed osteoporosis and 10(33%) cases had osteopenia in the lumbar spine, and 7(23%) showed osteoporosis in the hips. (Fig. 4)

Radiologic examination revealed 6 (20%) cases of vascular calcification revealed by aortic button calcification, the rest showing normal parameters. (Fig. 5)
Echocardiography was performed in 19 patients. It revealed a normal aspect of the valves and of the pericardium in 11 (58%) patients, thickened pericardium with calcifications in 1 (5%) patient, valvular calcifications in 2 (10%) patients, mitral ring calcification in 1 (5%) patient. (Fig. 6)

**DISCUSSIONS**

Our study has revealed the presence of phosphocalcic metabolism changes in 24 (80%) patients.

The phosphocalcic metabolism changes begin with decrease in calcitriol synthesis and phosphorus retention, which will determine decrease in seric calcium and hyperparatiroidism. An increased turnover of the bone thus occurs. The high prevalence of traditional risk factors for atherosclerosis, combined with factors specific to uremia can be responsible for the increase in vascular calcifications observed in these patients.

Alteration of the function of the vascular endothelium is one of the elements that lead to atherosclerosis. In the renal disease, endothelial dysfunction is present at the level of the large vessels as well as of the small ones [17].

Experimental studies have suggested that the dysfunction of the microvascular endothelium is involved in the mechanisms leading to the advance of the renal disease which, in turn exacerbates the endothelial dysfunction, contributing to the acceleration of atherosclerosis [18]. Renal failure causes changes in the plasmatic components and in the endothelial structure and function, which favors vascular lesion and inflammatory response.

Dyslipidemia associated with chronic renal disease participates in the inflammatory response in chronic renal failure.[19, 20]. In our study dyslipidemia was present in 11 (37%) patients.

Inflammation in chronic renal disease may play a central role in the predisposition of patients with chronic renal failure to vascular calcifications [21].

Inflammation is a basic component of the process of atherosclerosis and the increased seric levels of the inflammation markers, especially C–protein, are present in patients with renal failure in predialytic stage. [22] About 30-50% of the patients with chronic renal disease show increased seric values of the inflammatory markers. [23, 24] The rise of the mediators of inflammation is due to oxidative stress [25].

The progressive deterioration of the renal function in chronic renal disease leads to dyslipidemia and accumulation of uremic toxins which stimulate oxidative stress and inflammation that, in turn, may contribute to endothelial dysfunction and the advance of atherosclerosis.

In our study, reactive C protein levels were increased in 80% (24) of patients.

Some recent studies suggest that the anomalies of the phosphor-calcic metabolism, including calcium therapy, which may affect the balance of total calcium in the body may influence the development and advance of vascular calcifications. The correlation between vascular calcifications and the phosphocalcic product has been observed in the studies involving young patients with
chronic renal failure in pre-dialytic stage (in whom the vascular calcifications of the mean predominate) but not in the studies involving elderly patients with chronic renal failure in pre-dialytic stage, who also concomitantly show calcifications at the level of the intima. [26, 27, 28, 29]

In our study the phosphocalcic product was increased in 47% (14) of the patients.

From a physiopathological point of view, the increased level of phosphocalcic product is the most important mechanism involved in the calcification of the arterial media in patients with chronic renal disease alongside of age and diabetes.

It has been found that not all the patients with renal failure in pre-dialytic stage with comparable age, phosphocalcic product and type of nephropathy develop progressive vascular calcifications. Depositing of calcium and phosphorus at the level of soft tissues is the result of a complex interaction between a variety of local and systemic factors.

The increased phosphocalcic product associated with precipitation may contribute to calcification of soft tissues, but calcification of the media blood vessels is due to an active transport Na-P – dependent.

The role of PTH in the calcification of the arterial wall media is uncertain.

Vitamin D treatment may aggravate vascular calcification but it has not been yet proven that this is due to a corresponding increase in the seric concentration of calcium and phosphorus.

In our study, 21 (70%) patients underwent calcium treatment. The mechanisms involved in the vascular in the vascular calcifications in chronic renal disease include precipitation of calcium and phosphorus in the presence of excessive extracellular concentration [30, 31].

Depositing of calcium and phosphorus at the level of the atheroma plate may be focal and irregular (calcification of the intima) or diffuse at media level. Frequently, these two forms may be in combination. The atheroma plates of the uremic patients are much more frequent and more intensely calcified as compared with those of non-uremic patients [32]. The most important difference between uremic and non-uremic patients does not consist only of the size of the atheroma plate but particularly as regards its composition. Calcification of the media becomes visible on radiologic examination only after it has reached at a certain degree of intensity. Calcification of the media is a manifestation of ageing, and, from the perspective, the uremic status may be considered a status of premature and accelerated ageing. Calcification of the intima has a more serious prognosis than that of media [33].

Vascular calcifications may be observed in both the intima and the tunica media. Calcifications of the intima are specific to arteriosclerosis. Lesions of the intima, in advanced stages, lead to a narrowing of vascular lumen and to compromising of blood circulation, causing ischemic lesions and necroses. Calcification is an integral part of the process of arteriosclerosis, being present in 80-90% of atheromatous lesions [34]. In arteriosclerosis, vascular calcifications occur predominantly, at the level of the intima, in all its stages of evolution, being absent only in the very early stage [35]. Calcification of the media occurs in patients with chronic renal disease and end-stage renal failure and may appear independently in arteriosclerosis, involving etiological mechanisms different from these in calcifications of the intima [36].

Calcification of the media vascular wall increases vascular rigidity and diminishes vascular compliance. The hemodynamic consequences of the calcifications of the media of the arterial wall are totally different from those caused by arteriosclerotic calcifications [37]. Diminution of vascular compliance (reflected in increase in the velocity of the pulse-wave) may be contribute to increase in systolic blood pressure and increase in pulse pressure.

Recent studies have shown that advanced arteriosclerosis demonstrated by thickening of the arterial wall is present in patients with chronic renal disease before the beginning of hemodialysis treatment [38].

Studying a group of 60 patients with diabetic nephropathy and renal failure in pre-dialytic stage, Mehrotra noticed an increased prevalence and severity of coronary vascular calcifications as compared with the control group of diabetic persons with normal renal function [39]. In this population, the high degree of vascular calcifications did not correlate with changes in mineral metabolism.

In vascular calcifications in asymptomatic patients with normal renal function, the coronary calcium score advances at a mean rate of 33%/year [40]. The advance of coronary calcium score is twice higher in hypertensive and chronic renal disease patients as compared with hypertensive and normal renal function patients [41].

Calcification of the arterial wall media plays a dominant role in the advance of vascular calcifications in patients with renal failure pre-dialytic stage, while the advance of vascular calcifications in patients with normal renal function in particular reflect the evolution of calcification of arteriosclerosis [42].
Coronary calcifications are strongly correlated with calcifications present in the aorta (thoracic and abdominal aorta) and at the level of aortic valves, a fact that suggests a shared physiopathologic mechanism of this process [43, 44].

In our study, we detected extraskeletal calcifications in 10 (33%) patients: at the level of the aortic button, in 20% (6) of the patients, objectivized by thoracic radiography. Cardiac calcifications were found in 4 (21%) patients. Valvular calcifications were noticed in 10% (2 patients), calcifications of the mitral ring in 5% (1) patients and pericardic calcifications in 5% (1) of the patients, as revealed by echocardiography.

Eccocardiography, is a sensisitve method for detecting valvular calcifications [45]. Epidemiological studies carried out on elderly persons and menopause women have proven a reverse correlation between bone mineralization and vascular calcification. It has been proven that patients with osteoporosis shown an increased level of osteoporosis as well as of coronary artery calcifications [46, 47, 48, 49, 50].

The ability of the bone be mineralized reaches a peak between ages 25 and 35. Calcification of coronary arteries advances from the ages of 25-35 to before death [51]. By studies on animals (rats), Druke and Wallin have proven a relationship between bone demineralization and vascular calcification.[52, 53]

In our study, osteoporosis was present in 10 (33%) patients. Like arteriosclerosis, osteoporosis is associated with age, smoking, diabetes, inactivity and hypercholesterolemia [54]. Osteopenia was present in 10 (33%) patients. Osteoporosis and arteriosclerosis tend to be present in the same patient.

Directing patients with renal failure in pre-dialytic stage, attended to in proportion of 80% by family doctor’s offices, to the hemodialytics center reflects the fact that patients have increased compliance. Correct attendance of patients allows monitoring of the phosphocalcic metabolism and of its changes, as well as a correct treatment of the latter.

Only a percentage of 20%of the patients with chronic renal failure in pre-dialytic stage contact the hemodialysis center for initiating the therapy of substituting the renal function through the emergency service without previous attendance by family doctor’s offices.

Our study has revealed the fact that affection of the phosphocalcic metabolism is present in patients with renal failure in pre-dialytic stage. Knowledge of the changes that occur in the phosphocalcic metabolism in patients with renal failure in pre-dialytic stage is important for its correct treatment. Therefore, this study directs our attention towards the vascular and cardiac changes in these patients, offering us the possibility of a correct treatment of arteriosclerosis and of extraskeletal calcifications.

CONCLUSIONS

Assessment of bone lesions on initiation of renal function substitution therapy by dialysis is indispensable through several parameters regarding the therapeutic conduct and also due to the fact that the perturbation of the mineral and bone metabolism is important risk factor as regards the morbidity and mortality of patients with chronic renal failure.

REFERENCES

REFERENCES (CONTINUED)


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