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# TREATMENT OF RENAL OSTEODYSTROPHY IN PATIENTS WITH TERMINAL CHRONIC FAILURE TREATED WITH CHRONIC HEMODIALIZATION

**Healthcare**

**Keywords:** renal osteodystrophy (ROD), Enda Stage Renal Disease (ESRD), hemodialysis (HD).

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| **Qahil Ibraimi** | Faculty of Medical Sciences. University of Tetova. Republic of North Macedonia. |
| **Lutfi Zylbeari** | Faculty of Medical Sciences. University of Tetova. Republic of North Macedonia. |

**Abstract**

Renal osteodystrophy (ROD) presents a mineral-bone disorder as a consequence of mineral imbalance and bone metabolism that often occurs in patients with terminal chronic renal failure. Changes in uremic patients are manifested by ostalgias, phosphocalcemic pseudogout, muscle pain, frequent calcifications in soft tissues, calcifying phenomena, osteoporosis, osteitisfibrosis, amyloidosis, metabolic acidosis, which are frequent occurrences in patients with End-stage renal failure (ESRD) (Jürgen Floege, Richard F. et al.). The most important factors in the occurrence of ROD are: reduced elimination of urinary phosphorus with hyperphosphaturia, with increased concentration of phosphate in the blood (hyperphosphatemia), vitamin D deficiency, hypocalcemia and increased parathyroid hormone (PTH). (Gutierrez O, Isakova T, Rhee E, et. al.). Objectives of ROD treatment in patients with terminal chronic renal failure CTRF treated with chronic hemodialysis (HD) are: maintaining blood calcium and phosphorus levels as close to normal as possible, prevention of the development of hyperplasia and secretion of parathyroid hormone (PTH), prevention of extraskeletal calcium deposition and preventing the accumulation of aluminum and iron that can adversely affect the skeleton. Recently, the latest instructions of the foundation of K/DOQI (Kidney Disease Outcomes Quality Initiative) suggest 1,2 gr protein /kg body weight for patients with HD. More than 90% of patients on dialysis use phosphate binders (calcium carbonate, calcium acetate) to reduce the amount of phosphorus absorbed to reach normal levels of serum phosphorus from 3.5-4.5 mg / dl.

**PURPOSE**: the paper aimed to document and verify the prevalence of ROD submission in patients with ESRD treated with chronic HD bicarbonate, with duration of HD treatment over 72 months and frequency three times a week from 4.5 hours randomized by gender, mean age, and nationality.

**MATERIAL AND METHODS:** In the time-perspective study (cross-section) a total of 87 patients were involved (of which 42 (48%) with average age-55,00-10.00 old were female, while 45 (52%) were male with average age 12.00 years of 57.00) with ESRD treated with chronic HD with duration of HD treatment over 72 months and frequency three times a week from 4.5 hours with bicarbonate dialysis, with chronic HD over 96 months. To all patients were examined concentrations of calcium, phosphorus, magnesium, alkaline phosphatase and parathyroid hormone (PTH). In patients who were noticed symptoms of ROD we also did radiological examination of the skeleton.

**STATISTICAL PROCESSING:** from basic statistical methods were used: arithmetic mean value and standard deviation X ± SD. Comparative statistics of examined parameters was analyzed with the so-called Studentov test 't'. Statistical significance of differences between groups of patients was analyzed with the so-called "Anonova Two-Factor" test with statistical value for p less than 5%, respectively p <0.0005.

**CONCLUSION:** Treatment of ROD should be started in the early stages of chronic renal failure in order to prevent later complications. The disease should be treated with medications of calcium, vitamin D, PTH, phosphorus, dietary supplements and dyalysate solutions with the right amount of calcium depending on the disease. Since ESRD is an irreversible disease (in the absence of kidney transplantation), the duration of therapy should be long-term to prevent further complications of ROD.

## INTRODUCTION

The term "renal osteodystrophy" first came into use in 1943, when experts noticed a link between bone damage and chronic kidney failure (Cozzolino M, Ureña-Torres P, Vervloet MG, et al. & Moe S, Drueke T, Cunningham J, et. al). Renal osteodystrophy is a broad term consisting of biochemical disorders (in levels of calcium, vitamin D, inorganic phosphorus, parathyroid

hormone, bone mineralization, and soft tissue calcifications). A larger number of studies on ROD have verified that the above symptoms begin to manifest when Glomerular filtration rate (GFR) is <60mL/min/1,73m2 (Ho LT, Sprague SM). The highly positive correlation of mineral-bone disorders in patients with chronic renal insufficiency were described 60 years ago. (Follis RHJ, Jackson DA. & Pappenheimer AM). Phosphorus retention, decrease in the level of calcitriol in the blood, decrease in serum ionized calcium level, reduced number of vitamin D receptors and calcium sensors in the parathyroid gland and skeletal resistance to the calcium action of parathormone play a major role in the development of ROD. RODosteodystrophy (mineral-bone disorders) may be unavoidable in uremic patients treated with chronic hemodialysis therefore proper management and treatment in the initial stages and in time can significantly help alleviate the symptoms of this common phenomenon which is manifested in this group of patients. Processes and manifestations of ROD degree in patients with ESRD vary and are often dependent on the state of bone circulation which leads to increased rate of resorption and bone formation. Increased parathyroid hormone (PTH) levels and hyperparathyroidism (primary, secondary, tertiary) play a major role in the pathogenesis of conditions of high bone circulation.

The presentation of ROD in uremic patients treated with chronic hemodialysis is also influenced by: phosphate retention (high concentrations of phosphate in the blood-hyperphosphatemia) low calcium concentrations (hypocalcemia) which stimulates high secretion of parathyroid hormone, reduction of vitamin D (Calcitriol) concentrations, interleukins 1, 6 and Tumor Necrosis-faktor alfa (TNF-alfa. (Slatopolsky E, Gonzalez E, Martin K. & Hruska KA, Teitelbaum SL. & Elder G & Brandenburg VM, Floege J. & Sugimoto T, Ritter C, Morrissey J, et al.). Important factors that play a role in the pathogenesis of ROD are: osteomalacia, heavy metal intoxication, mainly aluminum, iron, diabetes, continuous ambulant peritoneal dialysis which leads to a large influx of calcium into the body through dialysis. Elder G. & Brandenburg VM, Floege J. & Sugimoto T, Ritter C, Morrissey J, et al.). In the pathophysiology of ROD the main ones are: two cells-osteoclast that cut or resorb bone and osteoblasts that build or form new bone. (Eriksen EF). Osteoblasts produce the organic bone matrix consisting of type 1 collagen along with other non-collagenous proteins such as alkaline phosphatase and osteocalcin (Aubin JE). The process begins with bone resorption by osteoclasts which are activated by osteoblasts through a complex of ligands RANK-RANK and are intricately regulated by several factors such as PTH, vitamin D, osteoprotegerin (OPG), etc. Factors that stimulate the complex and aim to increase osteoclast formation are PTH, vitamin D and acidosis. Interleukins such as IL-1, 6, tumor necrosis factor also activate osteoclasts. This will increase serum calcium levels by increasing bone resorption. Osteoprotegerin is an inhibitory factor of osteoclastogenesis and ultimately reduces bone resorption (Khosla S. Minireview). Low circulation conditions leading to impaired mineralization and the inability to repair any ongoing damage are more often symptomatic. This is observed in patients with dynamic bone disease, who have bone pain as the dominant symptom. In the advanced stages patients with ESRD and ROD present with bone pain or fractures. Low circulation conditions leading to damaged mineralization and inability to repair any ongoing damage. (Piraino B, Chen T, et al.). The highest incidence of fractures in these patients consists of poor structural integrity of the bone. Involvement of the proximal muscles and axial skeleton

comes as a direct consequence of aluminum toxicity and osteomalacia. Vascular calcifications are an important complication and can lead to area-specific manifestations. Vascular calcifications can increase wall stiffness and pulse pressure, along with chronic hypertension. This may result in a higher incidence of cardiovascular disease, cerebrovascular insult which is also counted as the main cause of high mortality of uremic patients treated with hemodialysis. (Moody WE, Edwards NC, et al.). The first and most important factor in the presentation of ROD is the reduced elimination of urinary phosphate (hyperphosphatemia) which worsens in parallel with the progression of chronic kidney disease. This is initially offset by an increase in parathyroid hormone, which affects the increase of urinary phosphate secretion, which is manifested by high phosphaturia. (Gutierrez O, Isakova T, Rhee E, et al.). ROD is defined as a systemic disorder of mineral and bone metabolism due to chronic kidney disease manifested by one or a combination of several anomalies as: 1) abnormalities in the metabolism of calcium, phosphorus, parthormon (PTH) or vitamin D; 2) abnormalities in bone circulation, mineralization, volume, linear growth, or bone strength; and 3) calcification of blood vessels or teeth. (Cozzolino M, Ureña-Torres P, Vervloet MG, et al. & 20. London GM & 21. Lui S, Chu H). ROD types are defined on the basis of bone circulation and mineralization and are manifested in the form of: osteitisfibrosa, osteomalaciation, osteoporosis, reduction of circulation and bone mineralization, adinamyc bone, chondrocalcinosis, osteopenia and bone fractures (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. & 23. Moe S, Drüeke T, Cunningham J, et al). In the clinical picture of ROD dominate: bone pain, joint pain of all bones, bone deformity, pathological bone fractures, general body weakness, skeletal deformity, symptoms of hypocalcemia, stomach pain, often also shortness of breath, convulsions, and impaired thinking. ESRD and treatment with chronic HD along with ROD is not only associated with bone fractures but also with cardiovascular and cerebral calcifications causing high mortality in uremic patients treated with HD, so-called syndrome: bone-vascular axis of the ESRD (London GM). Evaluation to be accurately obtained from current clinical, biochemical and radiographic imaging methods (including bone-mineral density measurement), bone biopsy has been and still remains the art standard for assessing the exact type of renal osteo-dystrophy, X-rays can also show the bone characteristics of renal osteodystrophy (subperiostic bone resorption, chondrocalcinosis of the knee and pubic symphysis, osteopenia and bone fractures) but can be difficult to distinguish from other rheumatic diseases. (Barsić, Neven: Cala, Kresimir, et al.).

## PURPOSE OF THE WORK

The paper aimed to document and verify the prevalence of ROD submission in ESRD patients treated with chronic HD bicarbonate, with duration of HD treatment over 72 months and frequency three times a week from 4.5 hours randomized by gender, mean age, and nationality.

## MATERIAL AND METHODS

In the time-perspective study (cross-section) a total of 87 patients were involved (of which 42 (48%) with average age-55,00±10.00 old were female, while 45 (52%) were male with average age 12.00 years ± of 57.00) with ESRD treated with chronic HD , with duration of HD treatment over 72 months and frequency three times a week from 4.5 hours, with bicarbonate dialysis with chronic HD over 96 months. To all patients were examined concentrations of calcium, phosphorus, magnesium, alkaline phosphatase and parathyroid hormone (PTH). In patients who were noticed symptoms of ROD we also did radiological examination of the skeleton.

## STATISTICAL PROCESSING

From basic statistical methods were used: arithmetic mean value and standard deviation X ± SD. Comparative statistics of examined parameters was analyzed with the so-called Studentov test 't'. Statistical significance of differences between groups of patients was analyzed with the so-called "Anonova Two-Factor" test with statistical value for p less than 5%, respectively p <0.0005.

**Table 1:** Presentation of patients by gender and mean age

| Gender | Number | Mean age ± SD |
|---|---|---|
| Male | **45 (52%)** | **57,00 ± 12,00** |
| Female | **42 (48%)** | **55,00 ± 10,00** |

**Table 2:** Presentation of patients according to nationality

| Total number =87 (100%) | Female | Male |
|---|---|---|
| Albanian - 60 | **25 (41%)** | **35 (59%)** |
| Macedonian - 27 | **11 (41%)** | **16 (59%)** |

## RESULTS

From 87 patients with ESRD treated with chronic intermittent HD, clinical, laboratory and radiographic symptoms of ROD were observed in 16 (13.3%) while in males from the total number -45 (52%) symptoms of ROD were observed in 20 (16.7%). All patients with ROD during HD sessions used dialysis solutions with a total calcium content (tCa) of 1.75mmol/l. Average values of plasma calcium and inorganic phosphorus (before HD sessions) to females ($N^0$=16) were: tCa=1.50±0.20 mmol/l, respectively for inorganic phosphorus (Pi)=1.95±0.80mmol/l, magnesium -1.04±0.40, Parathormon -260,00±18,00pg/mL while alkaline phosphatase was with values of -230.50±20.00 U/L which is above the reference values. Examined male patients ($N^0$=20) presented mean values of total Ca=1.60±0.10mmol/l, magnesium -1.07±0.30, phosphorite -1.90±0.90mmol/l, alkaline phosphatase -250±23.00U/L Parathormon (PTH)-230,00±16,00pg/mL while alkaline phosphatase was with values of -260.00±18.00U/L.

**Table 3:** Average values of Total Calcium (Cat), Magnesium (Mg) Phosphorous Inorganic (Pi), alkaline phosphatase and parathormone in patients with ROD.

| **Parameters** | **Cat** | **Mg** | **Pi** | **Alkaline Phosphatase (ALP)** | **PTH (pg/mL)** |
|---|---|---|---|---|---|
| **Female** | 1,50±0,20↓ | 1,04±0,40↓ | 1,95±0,80↑↑ | 230,50 ± 20,00 U/L, | 260,00±18,00 |
| **Male** | 1,60±0,10↓ | 1,07±0,30↓ | 1,90 ±0,90↑↑ | 250 ± 23,00 U/L, | 230,00±16,00 |

Mean values of total calcium (Cat) Magnesium (Mg), Inorganic Phosphorus (Pi), alkaline phosphatase and PTH in the ROD examination group were with a statistically significant difference for $p<0.0001$ compared to Cat-2,3±02,8 reference values; Mg -0.6-1.1, inorganic phosphorus (Pi) -0.8-1.4mmol / l, alkaline phosphatase = 3-140U/L and parathormone -11-67 ng/l. All patients were treated with Calcium Carbonate (CaCO3) preparations of 3.0–6.0g/day for uptake and binding of phosphorus from the intestine and substitution of Calcium deficiency, and intermittently (3x0.5μg/per week) were also treated with tablets Rocaltrol, Calcitriol (1,25/OH/$_2$ cholecalciferol) at doses of 0.25 and 0.5 micrograms three times a week, according to the severity of the disease given that the production between calcium and phosphorus should not be lower than 3.92-(Ca x Pi < 3.92).

## DISCUSSION

There is documented evidence that one of the complications of uremic patients treated with chronic hemodialysis is renal osteodystrophy (ROD) which consists of mineral-bone disorders (with osteitisfibrosa, arthralgia, osteoporosis, soft tissue calcifications or osteomalacia). ROD most often presents over time with HD treatment (in patients at the beginning of HD treatment is less pronounced, compared to patients with longer duration which presents with a higher percentage). ROD is diagnosed after the start of treatment of patients with ESRD with chronic HD. In the advanced stages laboratory blood tests show low concentrations of calcium and calcitriol (vitamin D), with an increase in blood phosphorus and a decrease in blood calcium (hypocalcemia) and high concentrations of parathyroid hormone (PTH). It is evident that in the early stages, calcium and phosphate concentrations are normal in favor of high parathyroid hormone levels and fibroblast -23 growth rate. In patients with ESRD and ROD, bone cells called osteoclasts and osteoblasts are not in physiological equilibrium. The way these bone cells go out of balance is when calcium, parathyroid hormone (PTH), phosphorus and activated vitamin D are out of physiological balance. Over time, and with HD treatment, ROD can cause bones to break easily, harden soft tissues of the body including calcifications of the vessels of the heart and brain. If Ca levels in uremic patients are very low the parathyroid glands (four small glands) secrete larger amounts of parathyroid hormone (PTH) which will begin to remove Ca from the bones to return Ca levels to normal. As the months and years go by, as calcium is removed from the bones, this condition can make the bones weak. Even high levels of phosphorus in the blood (hyperphosphatemia) affect the withdrawal of even more Ca from the bones, which consists in the bones starting to break down and losing structural ability.

However, vitamin D (calcitriol) also has a high impact on the appearance of ROD, which helps maintain normal PTH levels and balances calcium in the body. In patients with ESRD the conversion of inactive vitamin D to calcitriol is compromised and reduced which further favors the introduction of ROD.

The body is unable to absorb calcium from food so he 'borrows' the calcium he needs from the largest storehouse of calcium storage - your bones. ROD is often referred to as 'silent damage' because the symptoms do not appear in the early stages of the disease (the first years of HD treatment). Typical symptoms may be: bone pain, joint pain, bone deformity, bone fractures, poor mobility, etc. Early ROD indicators consist of high levels of phosphorus and/or PTH, redness of the eyes, itching and sores from calcium-phosphorus deposits. Renal osteodystrophy is manifested as a result of secondary hyperparathyroidism, hyperphosphatemia combined with hypocalcemia, which both manifest as a consequence of reduced phosphate secretion by damaged kidneys. Low activated level of vitamin $D_3$ is the result of the inability of the kidneys to return vitamin $D_3$ to its active form-calcitriol and results in hypokalemia. High levels of fibroblast growth factor 23 are thought to be the most important cause of low calcitriol levels in patients with chronic renal failure. During chronic renal failure excessive production of parathyroid hormone (PTH) increases the rate of bone resorption and in histological examination of bone mass verifies for diseases of secondary hyperparathyroidism. (Martin KJ, Gonzalez EA, et al. & Coyne DW, Grieff M, et al.). The initial growth of parathyroid hormone and bone remodeling can be greatly slowed down by a number of factors and treatments such as vitamin D, calcium salts, steroids and so on, leading to low bone circulation or adynamic bone disease. High and low bone circulation diseases are currently equally observed in patients with CKD treated on dialysis, and all types of renal osteodystrophy are associated with an increased risk of skeletal fractures, decreased quality of life and poor clinical outcomes. Secondary Hyperparathyroidism (HPT) is a common occurrence in patients with ESRD treated with chronic HD. HPT disorder is characterized by high levels of parathyroid hormones (with parathyroid gland hyperplasia) and disorders of Ca and Phosphorus metabolism (with hypkalemia and hyperphosphatemia) and Vit. D.

Distinctive sign of secondary hyperparathyroidism is increased osteoclastic activity with bone resorption when the cortical and trabecular part are gradually lost and replaced with connective tissue. Clinical overview in favor of renal osteodystrophy (ostalgias, phosphocalcemic pseudogout, muscle aches, frequent muscle calcifications, calcifying phenomena). Frequent resorptive changes in the cortical part of the bones observed by radiography, frequent calcifications of the visceral organs as well as calcifications in the tunica media of the arteries were observed in sixteen patients. From 120 patients with ESRD treated with chronic intermittent HD clinical, laboratory and radiographic symptoms of ROD were observed in 16 (13.3%) while in males from the total number-66 (55%) symptoms of ROD were observed in 20 (16.7%). All patients with ROD during HD sessions used dialysis solutions with a total calcium content (tCa) of 1.75mmol/l. Average values of plasma calcium and inorganic phosphorus (before HD sessions) to females ($N^0$=16) were: tCa=1.50±0.20mmol/l, respectively for inorganic phosphorus (Pi) =1.95±0.80mmol/l, magnesium -1.04± 0.40±, Parathormon -260,00±18,00pg/mL while alkaline phosphatase was with values of -230.50±20.00U/L which is above the reference values. Examined male patients ($N^0$=20) presented mean values of total Ca=1.60±0.10mmol/l, magnesium-1.07±0.30, phosphorite-1.90±0.90mmol/l, alkaline phosphatase -250±23.00U/L Parathormon (PTH) -230,00±16,00pg/mL while alkaline phosphatase was with values of -260.00±18.00 U/L.

Mean values of total calcium (Cat) Magnesium (Mg), Inorganic Phosphorus (Pi), alkaline phosphatase and PTH in the ROD examination group were with a statistically significant difference for $p<0.0001$ compared to Cat-2,3-02,8 reference values; Mg-0.6-1.1, inorganic phosphorus (Pi) -0.8-1.4mmol/l, alkaline phosphatase =3-140U/L and parathormone-11-67ng/l. All patients were treated with Calcium Carbonate (CaCO3) preparations of 3.0–6.0g/day for uptake and binding of phosphorus from the intestine and substitution of Calcium deficiency, and intermittently (3x0.5μg/per week) were also treated with tablets, Calcitriol ($1,25/OH/_2$ cholecalciferol) at doses of 0.25 and 0.5 micrograms three times a week, according to the severity of the disease given that the production between calcium and phosphorus should not be lower than 3.92-(Ca x Pi<3.92) results that are consistent with the literature consulted. To prevent ROD it is extremely important to maintain the concentration of phosphorus, calcium, PTH and vitamin D at normal levels even through a low-phosphorus diet also with the use of phosphorus binders (calcium carbonate, calcium acetate, zemplar, HCL calcimetriccinnacalcet (Sensipar/Mimpara) drugs that act directly on the parathyroid glands to block the release of parathyroid hormone, Rocaltrol and Renagel. (Gotch FA, KotankoP, et al.). The main goals of ROD treatment in patients with chronic renal failure treated with hemodialysis are: to maintain Ca and phosphorus levels in the blood as close to normal as possible, to prevent the development of parathyroid hyperplasia or to slow the secretion of PTH, to prevent extracellular calcium deposition, and to prevent or reverse the accumulation of substances such as aluminum and iron that may adversely affect the skeleton. Recently, new K/DOQI recommendations suggest a diet of 1.2g protein/kg body weight for patients treated with HD. In recent years it has been verified that aluminum hydroxide which was used as a phosphorus binder, because it causes neurological, skeletal and hematological toxicity in patients with ESRD treated with HD has been phased out. In the last decade, numerous studies on ROD have documented that the use of calcium salts as phosphate binders leads to an increase in mitral and aortic valve calcification in patients with ESRD treated with HD, therefore it is necessary to control the level of phosphorus in the serum and the values should be within 3.5-5.5 mg/dl and try to ensure that the total amount of calcium that patients consume (dietary calcium plus phosphate binders containing calcium) is not 12 g/day. Recently, new phosphate binders have been developed. One of them, Sevelamer (RenaGelR) is now widely used, and this phosphate binder is completely resistant to intestinal digestion and is not absorbed into the gastrointestinal tract. Studies have shown that this drug can effectively and safely lower serum phosphorus without altering serum calcium levels. The use of Calcitriol, Rocaltrol (the most active metabolite of vitamin D) has directly affected the parathyroid glands by suppressing the synthesis and secretion of PTH as well as by restricting the growth of parathyroid cells. The main toxicity of calcitriol is due to its potent effect in increasing intestinal absorption of calcium and phosphorus as well as because of the potential to mobilize calcium and phosphate from the bones. Hypercalcemia and/or hyperphosphatemia are common complications of such therapy that may limit its use in effective doses to suppress PTH. In the United States, intermittent intravenous administration of calcitriol is the common way to treat patients with hyperparathyroidism; however, researchers have administered oral calcitriol in an intermittent manner (oral pulse) with good results. Control of phosphorus levels in uremic patients treated with chronic HD is extremely essential, so recently the new recommendations of K/DOQI suggest that in addition to therapy, a diet of 1.2 g protein/kg body weight should be observed. Treatment of renal osteodystrophy in patients with ESRD and those treated with chronic HD aims to control the level of phosphate, calcium, vitamin D and Parathyroid Hormone (HPT). In cases with secondary hyperparathyroidism, total parathyroidectomy is preferred.

However, it is evident that in patients with ESRD treated with HD, kidney transplantation provides better treatment of ROD and other complications that manifest during uremia. In the treatment of ROD are used: treatment with phosphorus binders: Calcium carbonate, Calcium acetate, Sevelamer, Renagel, Lanthan carbonate, Aluminum Hydroxid, etc. Limitation of phosphates in food (especially inorganic phosphorus). Substitution with active forms of Vitamin D3 (Calcitriol, Rocaltrol, 1.25 or 0.5 microgram, alfacalcidol, paricalcitol, Tacacitol, doxercalciferol etc). Correction of Ca concentrations in Ca is regulated by the use of lower concentration dialysis.

## CONCLUSION

Treatment of ROD should be started in the early stages of manifestations in order to prevent later complications (cardiac valve calcifications, soft tissue calcifications, bone deformities, pathological fractures, bone demineralization, etc.). ROD in addition to medication can also be managed with dietary supplements and dialysis solutions with the right amount of calcium depending on the symptoms of the disease. Since chronic renal failure is an irreversible process (in the absence of kidney transplantation), the duration of therapy should be long-term to prevent further complications of ROD.

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