Review Article
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Idiopathic hypercalciuria presents: a precocious marker of osteoporosis

Abstract

Epidemiological studies in the last ten years have provided that nephrolithiasis is a risk factor for development of hypertension and have higher prevalence of diabetes mellitus and some hypertensive and diabetic patients are at greater risk for stone formation in connecting with altered calcium homeostasis; likewise in these last ten years, the deficit of zinc in the serum has been associated with the diabetes mellitus and another illnesses as: hipogonodism, Cushing Syndrome, celiac illness, and renal inadequacy, that propitiate to any age the osteoporosis appearance. It was used the creative idea as analysis method of data, applying the comparison by analogy between the well-known alterations of the homeostasis of the calcium and of the zinc, and those that can take place for the interaction among them. Review the data from the selected literature by this way, shows that, as conclusions: The event idiopathic calcium oxalate nephrolithiasis it is concomitant with the idiopathic hypercalciuria; the oxidative stress may be identifying by the presence of a direct correlation in the urine between the increments of calcium (hypercalciuria) and of zinc (hyperzincuria); the presence of idiopathic hypercalciuria it may be constitutes a precocious marker of the osteoporosis.

Keywords: normocalcemia, hypocalcemia, normozincemia, hypozincemia, oxidative stress, idiopathic hypercalciuria, hyperzincuria, primary and secondary osteoporosis

Volume 8 Issue 6 - 2019

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Received: September 23, 2019 | **Published:** November 08, 2019

Introduction

The osteoporosis is a mixed, very frequent bony atrophy, characterized by a reduction of the mass or of the volume of the osseous tissue, with relationship to the volume or mass of the anatomical bone, so much of the proteins that it constitute its womb as of the mineral salts of calcium that are deposited on the womb. The chemical composition of the porotic bone is normal, on the contrary of what happens in the osteomalacia. The spongy one offers the aspect of wide and scarce mesh of trabeculas and the cortical one is thin. Then, it diminishes the osseous mineral density in connection with the normal value, and the bone is less resistant and more fragile of the normal thing, it has less resistance to the falls and it breaks up with relative easiness after a traumatism, taking place fractures or microfractures.[1]

The determination of the bony mineral density is a useful marker for the diagnosis and the prevention of the osteoporosis; it is carried out with the technology of mensuration denominated osseous densimetry[2]. But, although at the moment the osseous mineral density by the norm WHO is a method very used for the diagnosis of the osteoporosis, it is necessary to have present that exhibits a poor sensibility in predicting potential fractures, if it is used as only medical mensuration.[3] But, on the other hand, the corresponding apparatus is the sufficiently expensive thing, in connection with the number of patients that it can be diagnosed in a day of sanitary work, like for not being frequently present in the policlinics in the system of the Primary Attention of Health. Thus, for not increase costs in the health, possible precocious markers of the osteoporosis should be located, such as mineral nutrients alterations which are present in bone, e.g. calcium and zinc, and them are determined by chemical tests that are part of the habitual schedule of a clinical laboratory; the alterations in calcium and zinc homeostasis it should be investigated at scenarios as for showing the secondary osteoporosis. The clinical manifestations of the osteoporosis only appear as consequence of their complications: the fractures.[3,4]

The osteoporosis can be, primary, constituting a common fact in the physiologic processes of, aging, with deficit of vitamin D3 because the old man is deprived from the solar benefit when avoiding the morning walks, and, postmenopausics, in this case to the decrease of the estrogens production by the ovarios;[5] and secondary, as a consequence of different endocrinometabolics illnesses as the hipogonodism, and the Cushing Syndrome, apparent in their clinical associations: obesity, arterial hypertension, diabetes mellitus (DM). Nevertheless, there is a considerable number of osteoporosis causes to any age that they are not usually recognized neither valued, among those that highlight, mainly, the celiac disease (CD), the renal inadequacy (causing of secondary hyperparathyroidism);and, the diabetes mellitus (DM), type 2. Associated to the previous pathologies which cause osteoporosis, [6] the oxidative stress (OS) has clinical presence;[7] the OS finds in the tabaquism and in the alcoholism favorable circumstances to its manifestación.[8] So, it has been proven that the oxidative stress (OS) it is presented as alteration in the serum homeostasis of the calcium and the zinc, when such a manifestation of OE is associated to the presence of osseous trabecular damage;[9] the discussion of the data are presented in the present paper finished section.

Background on calcium and zinc homeostasis

The calcium coming from the feeding is absorbed in the intestine and it goes toward the sanguine torrent, of where it passes to incorporate on the bone. Around 25mmol of calcium it enters in the organism in a normal diet. The bone is good as an important starting point for the storage of calcium, since it contains 99% of the calcium of the body. Nevertheless, all the calcium that arrives to the blood is not deposited to the bone, but rather in the blood a level of calcium remains in an interval of values that it characterizes its homeostasis. The normocalcemia (level of normal calcium in blood) it is closely regulated with some values of total calcium among 2,2-2,6mmol/L, and an ionized calcium of 1,1-1,4mmol/L. Around 40% (10mmol) of the ionic calcium it is absorbed by the long intestine, 5mmol is excreted through the fecal grounds, being a net quantity from 5mmol

of calcium to day. The vitamin D is an important co-factor in the intestinal absorption of calcium. The kidney filters around 250mmol/día of calcium, and it reabsorbs 245mmol, what gives a net total loss of approximately 5mmol/día (approximately 200mg of calcium in sample of urine of 24 hours). The kidney also metabolizes the vitamin D to the form active calcitriol (vitamin D3) that is more effective in the intestinal absorption. Both processes, of ossification (to incorporate calcium on the bone) and of bony resorption (to liberate calcium from the bone), they are stimulated by the vitamin D3. The calcium is liberated of the bone (bony resorption) for the hormone paratiroidea (PTH), while the calcitonin stimulates the incorporation of calcium in the bone (ossification). Around 5mmol of calcium it has a daily turn over on the bone.[10]

When the blood is filtered in the kidney there is a process of reabsorption of the calcium in the kidney that makes that that calcium returns to the sanguine torrent and of there to the bone, although there will always be calcium that is not reabsorbed in the kidney and it is eliminated by the urine. The hypercalciuria (value bigger than 200mg of calcium in sample of urine of 24 hours) it is the excessive excretion of calcium through the urine, generally associated to hypercalcemia (excess of calcium in blood that makes that, although the kidney reabsorbs calcium, it passes a lot of calcium to the urine). But it also exists a hypercalciuria associated to normocalcemia: the call idiopathic hypercalciuria; idiopathic that it means that the causes for those that the kidney doesn't reabsorb calcium are ignored (e.g., genetic). The term "idiopathic", applied to an illness, means that they don't know each other their causes. As in all hypercalciuria, due to the inadequacy of reabsorption of calcium in the kidney, an excess of excretion of calcium takes place through the urine, what can bear renal litiasis (calculations of calcic oxalate).[11] It is hypocalcemia to plasma calcium<2mmol/L.

The dependent protein-kinases of Ca2+/calmodulina (kinases CaM) they are the main mediators of the action of the Ca2+ like second messenger in the cells ß. In these pancreatic cells it meets an enzyme with activity of dependent kinase of Ca2+/calmodulina, the one which phosphorated proteins diverse, denominated kinase CaM II, located in the secretor granules of the cells ß, that which indicates the specific participation of this enzyme in the process of secretion of insulin. This process it inactive for cellular low concentrations of Ca2+, and it is activated for high concentrations of this cation. The CaM II are activated with high concentrations of glucose.[12,13]

The role of perturbations in the processes of calcium homeostasis differs with particular clinical scenarios.

As covered elsewhere in this series, zinc homeostasis is primarily dependent on an interplay between intestinal zinc absorption and excretion of intestinal endogenous zinc, with involvement of the kidney and bone (and possibly integument) contributing less prominently under normal circumstances. Absorption of dietary zinc is best characterized as a saturable process and is primarily determined by two factors: the amount of zinc ingested and dietary phytate. The zinc status of the host does not seem to be a major determinant of absorption efficiency. More responsive to host status is the excretion of intestinal endogenous zinc, which is normally conserved in the setting of marginal zinc absorption and provides a means to excrete excessive absorbed zinc.[14]

Over 85 percent of the total body zinc is found in skeletal muscle and bone.[15] While plasma zinc is only 0.1 percent of this total, its concentration is tightly regulated at about 10 to 20µmol/L. Stress, acute trauma, and infection cause changes in hormones (e.g., cortisol) and cytokines (e.g., interleukin 6) that lower plasma concentration. Small changes in tissue pools could cause the decrease. In human plasma zinc concentrations are maintained without notable change when zinc intake is restricted or increased unless these changes in intake are severe and prolonged.[16] Zinc secretion into and excretion from the intestine provides the mayor route of endogenous zinc excretion. It is derived partially from pancreatic secretions, which are stimulated after meals. Biliary secretion of zinc is limited, but intestinal, but intestinal cell secretion also contribute to fecal loss.[17] These losses may range from less than 1mg/day with a zinc-poor diet to greater than 5mg/day with a zinc-rich diet, a difference that reflects the regulatory role that the intestinal tract serves in zinc homeostasis. Urinary zinc losses are only a fraction of normal fecal losses.[15] The content of zinc in the urine is considered in 0,5-0,7 mg/día without being appreciated changes with the dietary load.[18] It is assumed for the hiperzincuria values bigger than 3mg/day in sample of urine of 24 hours.[19] Zinc transporter activity may account for renal zinc reabsorption and may glucagon help regulate it.[20] Increases in urinary zinc losses are concomitant with increase in muscle protein catabolism due to starvation or trauma. It is hypozincemia to plasma zinc<10µmol/L.

The action of the Zn2+ on the pancreatic cells ß, when their plasmatic concentration reaches levels bigger than the interval of 10-20µmoles/L, it determines an inhibition of the discharge of dependent action potentials of Ca2+ accompanied by a hiperporalización of the membrane potential. These facts suggest a paper regulator of the Zn2+ on the secretion of insulin, by means of a knot of negative feedback.[21,22]

The role of perturbations in the processes of zinc homeostasis, as for the homestasis of the calcium, differs with particular clinical scenarios. The study scenario presently research belongs together with that of the manifestation of the osteoporosis.

Alterations in calcium and zinc homeostasis at scenarios as for showing the secondary osteoporosis

The oxidative stress (OS) is caused by an imbalance among the production of the reactivate oxygenated species (ROS), peroxides and free radicals, and the capacity of a detoxification system and its two main antioxidation enzymes: Superoxide dismutase (SOD) and Glutathione peroxidase (GSH-peroxidase). Most of the ROS takes place in a low level in normal conditions of aerobic energetic metabolism and the damage that cause to the cells it is constantly repaired. If the detoxification system is overflowed, a situation of oxidative stress arises that if it reaches the tisular necrosis, it produces exhaustion of ATP impeding the cellular death for controlled apoptosis.[23] Several forms common of SOD exist: they are proteins with cofactors like copper, zinc, manganese, or iron. The absence of the enzymatic complex CuZnSOD accelerates the atrophy of the skeletal muscle, that is an characteristic event of the aging process.[24] The enzyme GSH-peroxidase catalyzed the oxidation reaction of glutation to glutation disulfuro using for it peroxide of hydrogen, that it detoxificated, transforming into water. This enzyme uses as cofactor selenio.[25] The maintained deficit of the concentrations of the transition metals and of the selenium, that it act as cofactors, they can allow the collapse of the detoxificación system.

Citation: Ramirez-Esteva OE, Malberty-Giro J. Idiopathic hypercalciuria presents: a precocious marker of osteoporosis. *MOJ Public Health.* 2019;8(6):218–221. DOI: 10.15406/mojph.2019.08.00310

Professor Krebs,[14] important pediatric nutriologist in the University of Colorado School of Medicine, has studied with extension and depth the deficit of zinc serum as consequence of different illnesses: hipogonodism, Cushing Syndrome (high level in cortisol serum that induces diabetes mellitus), diabetes mellitus (DM), type 2, celiac illness, renal inadequacy (causing of secondary hyperparathyroidism), it can show the secondary osteoporosis. The oxidative stress (OE) may be clinical presence.

If it considers these illnesses, one by one, as for alterations in the calcium and zinc homeostasis: hipogonodism, the hipogonadism is included between the signs and symptoms characteristic of the Deficit of Zinc Syndrome, with clinical registration of deficit of zinc in the serum.[26-28] Induced diabetes mellitus and diabetes mellitus type 2: diabetes is responsible for the increased urinary loss and decreases in total body zinc, thus the decreased of zinc in the serum affects the ability of the pancreatic islet cell ß to produce and secrete insulin, particularly in Type 2 DM, then appears to be a complex interrelationship between Zn2+ and both Type 1, and Type 2 diabetes: several of the complications of diabetes may be related to increased intracellular oxidants and free radicals associated with decreases in intracellular Zn2+, plasma Zn2+, and in Zn2+ dependent antioxidant enzymes;[29] celiac disease (CD), not surprisingly, zinc deficiency (on the basis of hypozincemia) has been reported in children and adults with CD,[30] and increased fecal and urine losses of endogenous zinc;[31] renal inadequacy, causing of secondary hyperparathyroidism, and it, alteration in the homeostasis of the calcium, then hipercalciuria, and finally litiasis, thus at hyperparathyroidism: the parathyroid glans segregate bigger quantity of parathyroid hormone (PTH), which regulates calcium level in the blood (calcemia) and the bone, then if in the normal physiology, when diminishing calcemia, the quantity of PTH increases to take calcium from the bones, in consequence an excessive production of PTH will give place to hypercalcemia, and to posteriori, hypercalciuria.[32,33]

Professor Khan,[33] recognized pathologist in the Florida University College of Medicine, by review of the recent literature indicates that production of reactive oxygen species (ROS) and development of oxidative stress (OS) may be such a common pathway; OS is a common feature of all cardiovascular diseases (CVD) including hypertension, diabetes mellitus, atherosclerosis and myocardial infarct. There is increasing evidence that ROS are also produced during idiopathic calcium oxalate (CaOx) nephrolithiasis.[34]

These illnesses connected by the Professor Khan occupy similar scenarios to those considered by the authors of the present article, with similar association in the environment of the oxidative stress. Both considerations extend to the pathology the category of interdisciplinary conceptual nucleus of the biomedical basic sciences assigned to the oxidative stress in a publication[34] of the authors of the present paper.

Evaluation of the alterations in serum and in the urine of the homeostasis of calcium and zinc

It was used the creative idea as analysis method of data, applying the comparison by analogy between the well-known alterations of the homeostasis of the calcium and of the zinc, and those that can take place for the interaction among them.

Then, by this way, and having present all above-mentioned in previous paragraphs, there is evidence that, event idiopathic calcium oxalate (CaOx) nephrolithiasis it is concomitant with the idiopathic hypercalciuria (alteration of Ca2+ in the urine taken place in normocalcemia).

On the other hand, some of the complications of the diabetes mellitus may be related to increased intracellular oxidants and free radicals associated with, decreases in intracellular Zn2+, plasma Zn2+, and in Zn2+ dependent antioxidant enzymes, and increased urine losses of Zn2+; in presence of oxidative stress there are increments in the urine of Ca2+ and of Zn2+ . Thus, may be identifying the oxidative stress, from the point of view of the clinical mineral chemistry in urine, by the presence of a direct correlation in the urine between the increments of calcium (hypercalciuria) and of zinc (hyperzincuria).

Then, it adding to the considerations of the previous paragraphs, the first conclusion of the investigation "Metabolic Disturbances in Calcium and Zinc, in associated with Progression Damage in Trabecular Bone",[9] that it points out that: "A sustained level of plasma zinc less than 10µmoles/L, in normocalcemia presence, it constitutes a factor of risk of osseous trabecular damage", it can become the third conclusion of the present work: The presence of idiopathic hypercalciuria (originated in clinical circumstances of normocalcemia) it may be constitutes a precocious marker of the osteoporosis.

Conclusion

The event idiopathic calcium oxalate nephrolithiasis it is concomitant with the idiopathic hypercalciuria. The oxidative stress may be identifying by the presence of a direct correlation in the urine between the increments of calcium (hypercalciuria) and of zinc (hyperzincuria). The presence of idiopathic hypercalciuria it may be constitutes a precocious marker of the osteoporosis.

Funding

None.

Conflict of interest

The authors declare that no financial or other conflict of interest exists between them or in relation to the content of the paper.

Acknowledgements

To the nutriologists, Professor Nancy F. Krebs, MD, University of Colorado School of Medicine, Aurora, USA, and Professor Aglae Cáceres-Diéguez, ScD, University of Medical Sciences School of Medicine 1, Santiago de Cuba, Cuba.

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Citation: Ramirez-Esteva OE, Malberty-Giro J. Idiopathic hypercalciuria presents: a precocious marker of osteoporosis. *MOJ Public Health.* 2019;8(6):218–221. DOI: 10.15406/mojph.2019.08.00310