# PARATHYROID GLANDS: STRUCTURE, FUNCTIONS AND PATHOLOGY

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**ABSTRACT**

The authors present a summary on the normal anatomy and function of the parathyroid glands as well as a brief review of clinical and pathological repercussions of higher and lower parathyroid hormone production. The emphasis is given on the causes, physiopathology, anatomy, macroscopy and microscopy of the lesions and their role in the genesis of fibrocystic osteitis, also known as Von Recklinhausen disease of the bones. Radiological correlation is also given. The authors show the challenges for the diagnosis in the same cases. We also write about secondary and tertiary hyperparathyroidism, as well as hypoparathyroidism.

***Keywords:*** *Hyperparathyroidism primary. Adenoma. Hyperplasia cystic fibrous osteitis. Neurofibromatosis 1.*

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## INTRODUCTION

Parathyroid gland is formed by four nodules originated from the third and fourth branchial arches, two at thyroid's right and left lobes apex and the remaining two on lower poles. Topography variations are common, because they are sometimes located next to larynx with no correlation to thyroid, and can be found up to mediastinum, next to thymus.[1] Each gland presents progressive growth up to the third decade of life, reaching a mean weight of 0.45 g in males and 0.5 g in females, with longest axis measuring 5mm.

Microscopically, they are constituted of main cells, clear cells and oxyphilous cells. The "main" cells are rounded with homogenous and slightly acidophil cytoplasm, producing parathormone. When secretion is lower or when at "rest" status, cytoplasmic granules of lipids and glycogen are accumulated, assuming characteristics of the so-called "clear cells".[2] "Oxyphilous" cells are larger, with acidophil cytoplasm because of its affinity to eosin, and appear in puberty, progressive increasing in number with age, do not release parathormone and its function is still unclear.[1-3] All cells are deployed on a rope-like arrangement, interposed by fat tissue lobules.

Parathormone is a protein with molecular weight of 8500 D[4], constituted of simple polypeptide chain with 84 amino acids. It is the antagonist of calcitonin produced by thyroid's parafollicular C cells. It acts directly on renal tubules cells inhibiting phosphates reabsorption and regulating phosphaturia. On bones, it acts on osteoclasts, which, by enzymatic action, reabsorb the matrix and turn calcium soluble. Parathormone, therefore, plays a critical role on bone turnover, i.e., on the balance between apposition and reabsorption, on keeping serum calcium levels around 8.9 to 10 mg/% and on calcium absorption on bowel. Calcium and phosphorus keep a ratio of 2:1, from hydroxyapatite crystals (tricalcium phosphate) to blood formula, which, under normal values, corresponds to 9mg/% calcium and 4mg/% phosphorus, whose product under normal conditions is 36 in adults and 40 in children. Upon changes on serum calcium or phosphorus levels, under parathormone action, a variable amount of minerals will be removed from bone to properly keep Ca/P balance.

Changes resulting from the lack or excess of each of the factors acting on bone apposition and reabsorption determine the so-called metabolic diseases of the bone, such as osteoporosis, childhood rachitis and adult osteomalacia, as well as hyperparathyroidism.

## PATHOLOGY

### HYPERPARATHYROIDISM

Hyperparathyroidism is the result of persistent hyper secretion of parathormone, and may be primary, secondary or tertiary.

### PRIMARY

Its primary cause of Parathyroid Adenoma, followed by Primary Hyperplasia and by Carcinoma. The first report on parathyroid tumors was provided by Askanazy[5] when performing an autopsy in a cystic fibrous osteitis. Albright and Reifenstein[6] described the parathyroid's clear cells hyperplasia, while Hall and Chaffin[7] provided the first description of parathyroid carcinoma. Castleman and Mallory[8] described gland changes in 25 hyperparathyroidism cases, and Pappenheimer and Wilnes[9] described secondary hyperplasia in renal diseases.

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## ADENOMA

It is the main cause of primary hyperparathyroidism, present in about 90% of the primary-form cases. It is more commonly found in adults, especially in females above the age of 50, at a ratio of 2:1. It is characterized by prevalent proliferation of main cells forming a tumoral nodule, usually isolated, rarely in more than one gland.[1] (Figure 1) Its prevalence on two glands is 6%[5]. It has a small size, weights 10g at most, and is 1-3 cm wide, well outlined by a connective tissue strap from the organ's capsule. When sectioned, the adenoma is homogenous, pinkish, and soft (Figure 1A). According to some authors, an adenoma's weight is proportional to the severity of hyperparathyroidism and bone changes, and may reach 50g or more.[10]

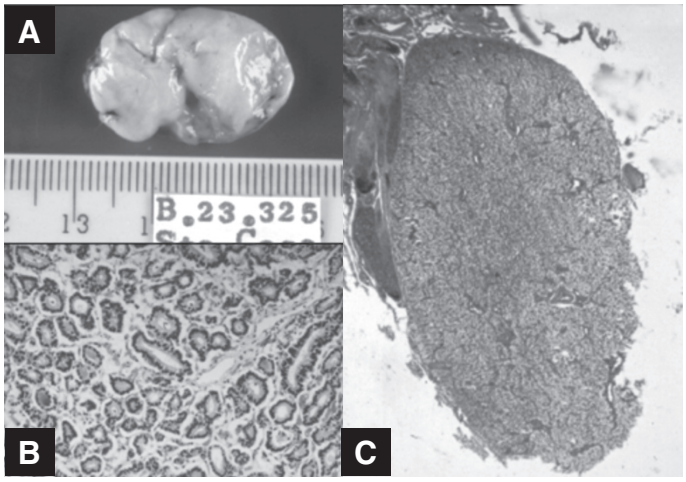


**Figure 1 –** *Parathyroid adenoma. A. Gross appearance: nodule with homogenous section surface. B. Microscopic appearance: gland is replaced by neoplasic proliferation. H.E.1O X*

Histologically, the adenoma is constituted of main cells, interposed by a variable amount of clear cells replacing the structure of the gland, which loses its traditional rope-like arrangement, because the cells are deployed as small blocks or in acinar arrangement, interposed by loose connective stroma with a rich capillary vascularization.[8,11] Normal fat tissue is scarce or inexistent (Figures 1B,C). The oxyphilous cells adenoma is rare and causes no endocrine effects.[3]

The disease is initially asymptomatic, and may be occasionally evidenced by routine laboratory tests.[12] Its clinical evolution is slow and progressive, with varied manifestations, ranging from nausea and diarrhea, gastrointestinal ulcers, repeated urinary calculus or gallstones, bone fractures with no apparent cause or by mild traumas, to psychic changes, accompanied by fatigue and neuromuscular weakness.[13] These changes depend on the evolution time, and may persist for years undiagnosed and untreated. Diagnosis must be made as early as possible, because, in late advanced cases, with serious bone injuries, it can be irreversible and deadly as a result of kidney failure.

When hyperparathyroidism is suspected, laboratory tests are warranted. The first biochemical sign is hyperphosphaturia, by the action of parathormone on renal tubules, inhibiting phosphorus reabsorption. For maintaining the calcium/ phosphorus product on the blood around 36 in adults an increased bone reabsorption will occur, which is translated into hypercalcemia, to 10 or more mg/%. As a result of hyperphosphaturia, hypophosphatemia of 3mg/% or less will occur. High serum parathormone dosages will confirm the presence of the disease.

Initial X-ray changes lay on hand phalanges as subperiostal reabsorption foci and on "lamina dura" of teeth implantation, where other reabsorption foci exist.

With disease progression, bone changes become increasingly evident, until they reach more severe stages. Subperiostal reabsorption foci start to compromise long bones (Figures 2A,B; 3A), and cystic lesions of variable sizes appear. (Figures 4A,B) Bones become increasingly weak, soft, showing increasingly severe fractures. (Figures 5A,B) Isolated or multiple cysts become quite evident on X-ray (Figure 4A) and on gross examination of the bones. (Figure 4B) As a result of reabsorption intensity, hemorrhage areas appear, assuming an X-ray appearance of epiphyseal or metaphyseal "tumors" (Figure 6), "brown tumor".

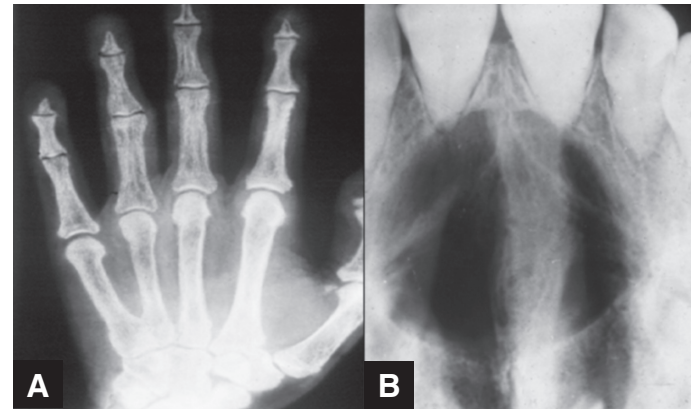


**Figure 2 –** *Parathyroid adenoma. A. and B. Normal parathyroid. The cells are arranged as straps interposed by fat lobes H.E. 60 and 110 X.* **C.** *and* **D.** *Adenoma: The cells are deployed as blocks or in an acinar arrangement H.E. 110 X and 240 X.*

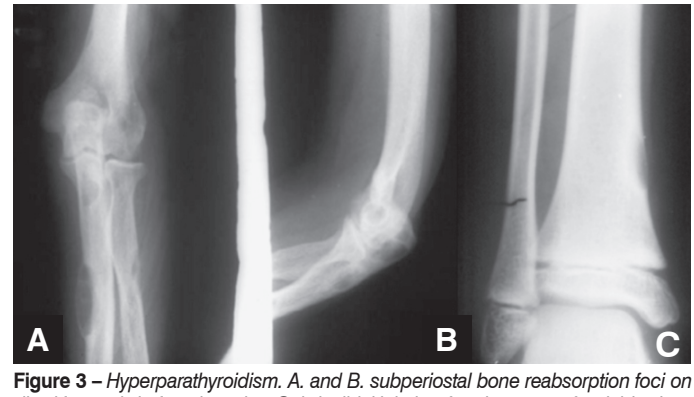


**Figure 3 –** *Hyperparathyroidism. A. and B. subperiostal bone reabsorption foci on distal femoral shaft and on ulna.* **C.** *lytic tibial injuries, forming cysts of variable sizes*

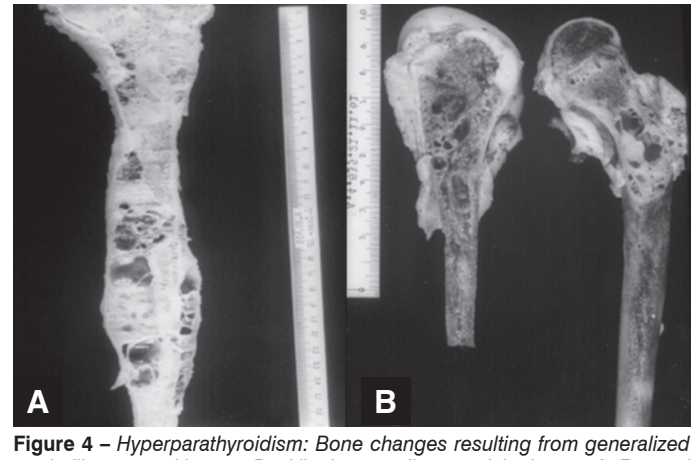


**Figure 4 –** *Hyperparathyroidism: Bone changes resulting from generalized cystic fibrous osteitis - von Recklinghausen disease of the bones. A. Femoral "softening". B. Irregular fractures.*

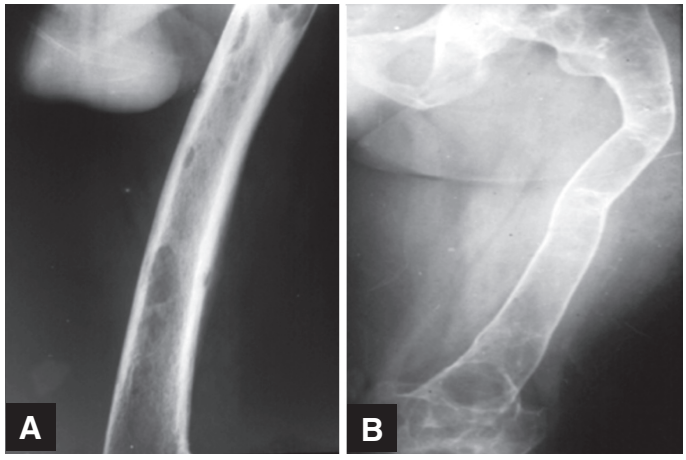


**Figure 5 –** *Hyperparathyroidism: Cystic Fibrous Osteitis. A. Tibia appearance on X-ray; where deformities, cystic lesions and sclerosis areas are seen; B. Gross tibial appearance, evidencing multiple cysts interposed by dense areas.*

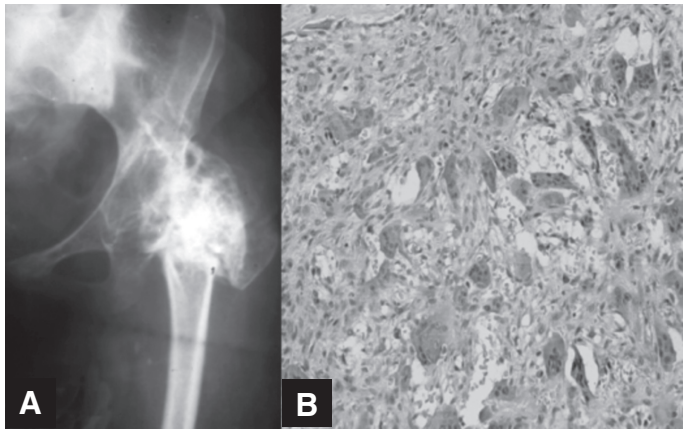


**Figure 6 –** *Hyperparathyroidism: Cystic Fibrous Osteitis: A. and B. Remnants of bone girders around fibrous proliferation;* **C***. Osteoclasts "front" around bone girder undergoing reabsorption.*

Microscopically, bones show a reduced girder thickness – osteoporosis – and reduced mineralization – osteomalacia – around fibrous proliferation. (Figure 7A) On bone girders' edges reabsorption gaps are numerous, with a variable number of osteoclasts, sometimes as "reabsorption fronts". (Figure 7B)[14] Lesions behaving as "brown tumor" on X-ray are the result of hemorrhagic foci, which, after red blood cells' disintegration, will make cumulative hemosiderin deposits to appear, permeated by numerous multiple nucleated giant cells with osteoclasts characters (Figure 6B), corresponding to "hyperparathyroidism brown tumors", which is pseudoneoplasic. Both on X-ray and on anatomopathological tests, it is similar to a true giant cell tumor, of which differential diagnosis in biopsies is not always easy. The potential for errors should be present and, should it occurs, it could lead to a disastrous therapeutic approach for the patient.[12]

X-ray and anatomopathological changes constitute a picture of generalized cystic fibrous osteitis or von Recklinghausen disease of bones.

Progressively, both clinical and anatomopathological renal changes will become increasingly severe and life threatening, because of nephrocalcinosis and resultant kidney failure. (Figure 8)

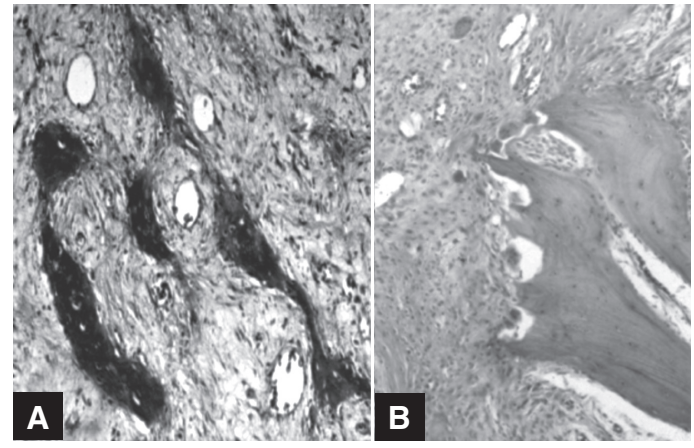


**Figure 7 –** *Of Hyperparathyroidism: "Brown tumor" A. "Tumor" on proximal femoral end; B. Several multiple nucleated giant cells, osteoclasts, around macrophages with hemosiderin.HE 120 X.*

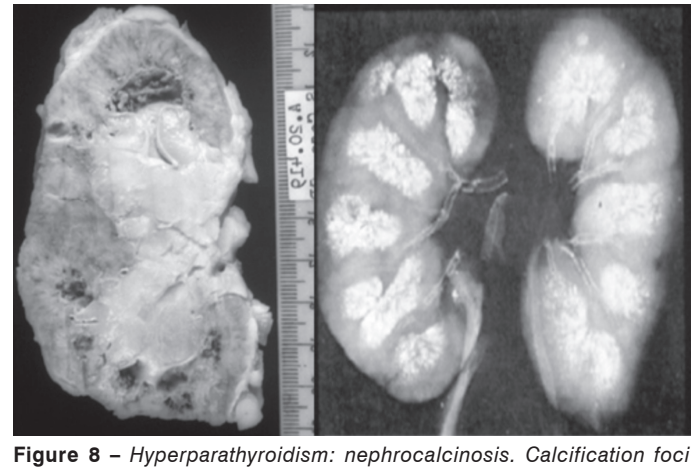

**Figure 8 –** *Hyperparathyroidism: nephrocalcinosis. Calcification foci disseminated on renal tubules. HE 120 X*

Due to the variety of clinical, laboratorial, X-ray and anatomopathological manifestations, we can say that primary hyperparathyroidism is a disease that must be know and recognized by doctors in general, regardless of their specialty area, so that they are aware for the fact that this is a benign disease, which, if diagnosed at early stages, is perfectly curable. It becomes incurable when bone and kidney lesions become irreversible, leading to a life-threatening condition to the patient.

A significant example of late diagnosis of this entity is the case illustrated on figures 9 and 10. This was a 60 year-old female patient who had a spontaneous femoral fracture when moving on bed. X-ray images evidenced osteolytic injury on femoral shaft. However, by assessing previous imaging studies to this fracture, which had been performed since 1962, evidenced other injuries, lytic as well, on hip, skull, leg and hand bones. On the femur, other injuries existed, documented by successive X-ray examinations, in addition to the fractured region. At that time, and until then, a supposed clinical and X-ray diagnosis of generalized carcinoma metastases was provided. Many other clinical and laboratory tests were performed throughout these years, but essential calcium and phosphorus counts were not performed. The disease evolved to progression of lesions on skeleton. In 1992, thirty years later, the patient was examined

by us, and we requested calcium, phosphorus and alkaline phosphatase counts, which were extremely altered, as well as parathormone. The patient was submitted to parathyroid nodule resection and femoral fixation, the fracture on which united within two months with regression of other injuries, so eager her bone tissue was for calcium. For some time, endovenous calcium replacement was required, with the overall improvement of the patient. (Figure 10)

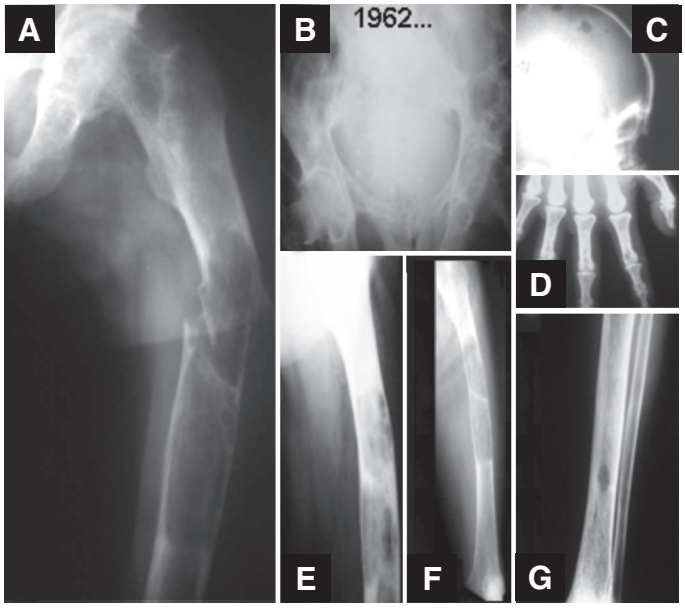


**Figure 9 –** *Hyperparathyroidism. 62 year-old female patient.A. Fracture on osteolysis area on femoral shaft. B.,C. and D. Several generalized osteolytic lesions, existing since the patient was 32 years old.. E.F. Injuries increased by number and size, when the patient was 62 years old.*

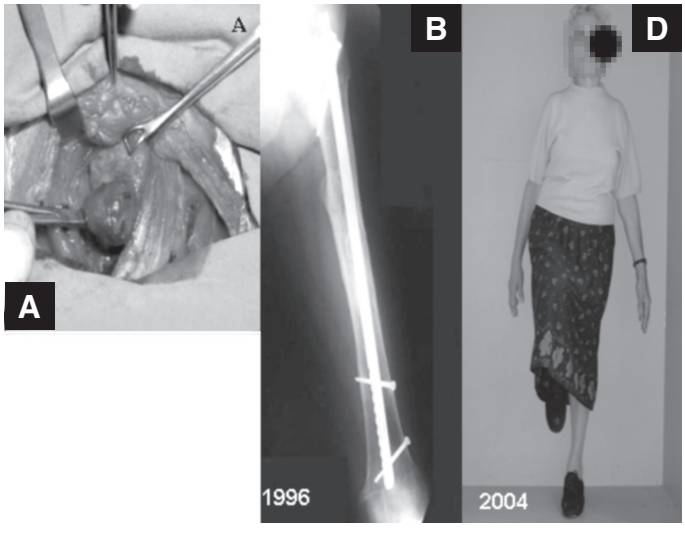


**Figure 10 –** *Hyperparathyroidism. 62 year-old female patient. A. Parathyroid nodule during surgical procedure. B. Fracture reduction. C. The patient, two months after parathyroid nodule resection.*

Physiopathology: bone tissue shows no interstitial growth. It grows under the expense of the apposition of a new matrix over the previously existent one, by osteoblastic activity, which produced the matrix. These cells are identical to fibroblasts that produce collagen fibers on soft tissues. On bones, the collagen of the matrix has the ability to mineralize by depositing hydroxyapatite crystals, which, under normal conditions, does not occur on other tissues. Matrix reabsorption is performed by osteoclasts, syncytia forming on bone marrow having characters of multiple nucleated giant cells. Osteoclasts act under direct stimulus of the parathormone and local agents such as the alpha factor (TGF alpha), tumor necrosis factor and interleukins.[15] About 95% of bone matrix is constituted of collagen fibers. The remaining 5% are on cement or reverse lines, which mark the apposition ranges over the pre-existent ones, constituted of glycosaminoglycans (hyaluronic acid and chondroitin sulfate). Several factors contribute to matrix formation and maintenance, especially an appropriate protein intake, vitamins A and C, hormonal stimuli of hypophysis, thyroid, supra-renal, gonads, and muscular activity, which is essential for osteoblastic activity. Matrix mineralization depends on nutritional factors such as calcium and vitamin D intake, sun rays and normal bowel activity for calcium absorption, also under parathormone action.

Bone turnover, apposition and reabsorption, persists throughout life. It is higher during intra-uterine and first decade of life, becoming progressively lower with aging, but always present until older ages. The skeleton is an important metabolic homeostasis factor for proteins and minerals in our body.[12]

Parathormone in excess will cause unbalance on bone maintenance, acting on osteoclasts that, through enzymes (hyaluronidase and collagenase), absorb the matrix and make calcium soluble.

Treatment consists of surgical removal of the parathyroid with adenoma. For being an slow-progression disease that could remain for years, the surgical removal of parathyroid can provide a definitive cure and changes regression. If bone repercussions and renal changes due to nephrocalcinosis are very severe, the patient can die. (Figure 8)

## HYPERPLASIA

This is an increase of the number of cells in one or more parathyroid glands, rarely in all four, and is the second most frequent cause of primary hyperparathyroidism, found in as many as 7% of the cases[13], of unknown etiology. In most cases, main cells proliferation is seen, with a variable amount of clear and oxyphilous cells. At early stages, cells are arranged as small isles, which progressively replace the gland as ropes or with an acinar arrangement, with increased size and weight. The histological differential diagnosis with adenoma, when examining only one gland, is particularly difficult, is not indistinguishable, especially if the test is made through freeze biopsy during surgical procedure.

Not rarely, primary parathyroid hyperplasia is included on type-I multiple endocrine tumors picture, when associated to Langerhans'isles tumor of the pancreas and hypophysis tumor, and on type-II, when associated to medullary thyroid carcinoma and to the medullary pheochromocytoma of supra-renal gland.[13]

## CARCINOMA

It is the cause of primary hyperparathyroidism in about 2.9% of the cases.[13] The criteria for microscopic diagnosis of parathyroid carcinoma should be well assessed by the anatomopathologist. Only a disarrangement and cell and nucleus polymorphism with mitosis are not absolute elements for diagnosis. The organ capsule

invasion and the appearance of atypical mitosis characterizing anaplasia, as well as the identification of neoplasic cells in the lumen of blood and/ or lymphatic vessels[13] contribute to the diagnosis. Sometimes, these criteria are not enough to differentiate adenoma, which, in some cases, shows a marked cellular polymorphism, inducing a wrong diagnosis of carcinoma. Certain cases diagnosed as adenoma only started to be interpreted as such after patient's evolution with metastasis to lungs.

## SECONDARY

Hormone hyper secretion is regarded as secondary when resulting from extra-glandular stimuli, especially those related to a lower calcium ions concentration on blood, so as to provoke parathyroid cells proliferation in order to, with a larger amount of circulating hormone, remove from bone the amount of mineral content for maintaining calcium/ phosphorus balance on blood.

Chronic kidney diseases are the major causes for such metabolic changes, because the impaired glomerular filtration determines a decrease on the conversion of the 25-hydroxycalciferol into 1.25 2-hydroxycholecalciferol, the active form of vitamin D. The reduction of this vitamin will lead to a lower calcium absorption by bowel, resulting in a stronger stimulus to parathyroid, an effect worsened by the heightened phosphorus retained on blood.

The bone changes resulting from this metabolic dysfunction are called "renal osteodystrophy" (renal rachitis) where the excess of parathormone would induce a double action on the bones, accelerating reabsorption with an increased osteoclasts activity and formation of a new bone by osteoblastic stimulus.[14,16]

On X-ray studies, areas of more or less condensation are seen, which, at gross examination, are characterized by thinner (osteopenia) and demineralized (osteomalacia) bone girders. Brown tumors are rare.[17]

Less frequently, these changes are seen in cases of bone resistance to parathormone action and in malabsorption syndromes of the bowel.[18]

## TERTIARY

Despite of controversies, hyperparathyroidism is regarded as tertiary when caused by autonomous proliferation of cells in patients with secondary hyperparathyroidism developing to hypercalcemia at the reestablishment of renal function 12.

## CRITERIA

1) confirmed renal disease followed by hypocalcemia;
2) hypercalcemia resistant to dialysis or transplantation;
3) subsequent calcemia return to normal levels after parathyroidectomy.

The mechanism is still unclear.[19] Molecular studies suggest that the progression of tertiary hyperthyroidism is associated to the loss of chromosome allele[4], consistent with monoclonal proliferation that is found with previous parathyroid hyperplasia.

## HYPOPARATHYROIDISM

This is characterized by a persistent reduced release of parathormone, followed by hypocalcemia and hyperphosphatemia.

Its main symptom is the increased neuromuscular excitability, well evidenced by Chvostek sign at facial nerve percussion. When it is more severe, it can evolve to tetany. Psychic and neurologic changes may occur, as well as anomalous intracranial calcifications and other changes related to the severity of hypoparathyroidism. The main causes in adults are the inadvertent surgical removal of parathyroid glands in thyroidectomies or in cases of lymphadenectomies of carcinoma metastasis on cervical region. Other rarer causes have been pointed out, such as post-radiation and suppression of parathormone production in cases of prolonged hypercalcemia. In children, cases of idiopathic hypoparathyroidism and familial auto-immune forms are mentioned.[13]

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