The assay of the hypocalcemic PTH fragment inhibitor with PTH provides a more accurate assessment of renal osteodystrophy compared to the intact PTH assay

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SUMMARY

As the chronic kidney disease patient is being managed for PTH, calcium, phosphate, vitamin D, calcium × phosphate product and bone quality an accurate PTH measurement is essential. Over and under PTH suppressive therapies pose significant risks of mineral metabolism disturbances, osteodystrophies and soft tissue calcifications. Until recently it was thought that there was only one hormone secreted by the parathyroid gland, 1-84 PTH (or CAP). It is now known that there is another hormone secreted by the parathyroid gland (CIP) which is most likely 7-84 PTH. 7-84 PTH has been demonstrated to be an antagonist of 1-84 PTH with inverse biological activities. 7-84 PTH has been demonstrated to be hypocalcemic and able to lower bone turnover through an inhibition of osteoclast formation resulting in an overall inhibition of bone resorption. Whereas, 1-84 PTH operates through the PTH/PTHrp receptor the 7-84 PTH appears to operate through a C terminal PTH receptor. The CAP/CIP ratio decreases in the dialysis patient when calcium increases and vice versa. The 2nd generation «intact» PTH assays measure the sum of CAP plus CIP which render them ineffective at predicting bone turnover (72% predictive) and monitoring PTH suppressive treatments. By contrast the CAP/CIP ratio predicts bone turnover in the dialysis patient with a histologically determined 93% predictability. An elevated CAP/CIP ratio indicates high bone turnover and a decreased CAP/CIP ratio indicates adynamic low bone turnover.

Key words: ***7-84 PTH. 1-84 PTH. Intact PTH.***

EL FRAGMENTO HIPOCALCÉMICO INHIBIDOR DE PTH PROPORCIONA UNA MEDIDA MÁS PRECISA DE LA OSTEODISTROFIA RENAL EN COMPARACIÓN CON LA DETERMINACIÓN DE LA PTH INTACTA

RESUMEN

La PTH, calcio, fosfato, vitamina D, producto calcio-fósforo y calidad ósea se utilizan para el manejo del paciente con insuficiencia renal crónica, por lo que la precisión en la medida de la PTH resulta esencial.

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Las terapias de supresión de PTH, tanto en exceso como en defecto, suponen riesgos importantes de alteraciones en el metabolismo mineral, osteodistrofia y calcificaciones de tejidos blandos. Hasta hace poco se pensaba que había solo una hormona secretada por la glándula paratiroidea, la 1-84 PTH (o CAP). Se conoce que existe otra hormona secretada por la glándula paratiroidea (CIP) que probablemente es el fragmento 7-84 de la PTH. Este fragmento ha demostrado ser un antagonista del fragmento 1-84 de la PTH con actividades biológicas contrarias. El fragmento 7-84 PTH ha demostrado ser hipocalcémico y con capacidad de disminuir el remodelado óseo a través de una inhibición de la formación de osteoclastos y como consecuencia una inhibición de la resorción ósea. Mientras que la función del fragmento 1-84 se realiza a través del receptor PTH/PTHrp, el fragmento 7-84 de la PTH se cree que utiliza un receptor C terminal de PTH. La proporción CAP/CIP desciende en los pacientes en diálisis cuando incrementa el calcio y viceversa. La PTH «intacta» de segunda generación mide la suma total de CAP más CIP, lo cual hace que resulte inefectiva en la predicción del recambio óseo (en un 72%), así como, en la monitorización de la PTH en los tratamientos supresores. En contraposición, la proporción CAP/CIP predice el recambio óseo en los pacientes en diálisis determinado histológicamente con una predicción del 93%. Una proporción CAP/CIP elevada indica un alto recambio óseo y un descenso en la proporción CAP/CIP indica un bajo recambio óseo adinámico.

Palabras clave: ***PTH fragmento 7-84. PTH fragmento 1-84. PTH intacta.***

Parathyroid hormone or 1-84 PTH with its 84 amino acids has more than 20 actions throughout the body including actions on the bone, kidney, gut, nerve cells, cardiovascular cells, etc.[1]. In managing the direct and indirect complications of renal osteodystrophy the most important actions of PTH are those that relate to the control of mineral metabolism, especially calcium metabolism. Since 98% of the body's calcium resides in the bone, the actions of PTH on the bone have been extensively studied. 1-84 PTH increases bone turnover and serum calcium after first binding to the PTH1R receptor on the bone and other target organs. However, PTH is not the sole determinant of serum calcium. The metabolisms of calcium, phosphorus, vitamin D and PTH are all intricately interrelated through complex biofeedback mechanisms. PTH also has a broad spectrum of actions to raise calcium. For example, PTH brings about its calcium increasing actions by stimulating bone resorption, the production of $1,25(OH)_2D_3$ and causing the gut to increase its absorption of calcium.

The first stage of renal osteodystrophy is the onset of secondary hyperparathyroidism. Secondary hyperparathyroidism is termed secondary because it is a secondary disease that follows impairment of kidney function. This occurs as kidney failure results in an increased accumulation of serum phosphate. This increase in phosphate drives the body to lower calcium. This decrease in calcium stimulates the parathyroid gland to produce 1-84 PTH which results in an overall hyperplastic condition of the parathyroid gland. Kidney failure also results in a decreased production of the active form of $1,25(OH)_2D_3$ which also directly inhibits the production of 1-84 PTH and decreases the absorption of calcium from the gut bringing about hypocalcemia. Clearly the most serious consequences of secondary hyperparathyroidism for the ESRD patient are renal osteodystrophy and mineral metabolism abnormalities which result in deterioration of bone turnover and quality and soft tissue/vascular calcification. For these reasons, the control of secondary hyperparathyroidism in the ESRD patient is of paramount importance to avoid the devastating effects of bone disease and soft tissue/vascular calcification. Early control of secondary hyperparathyroidism is essential in order to avoid progression to tertiary hyperparathyroidism in which the parathyroid gland functions autonomously to the actions of calcium and vitamin D. Tertiary hyperparathyroidism leads to severe hypercalcemia, hyperphosphatemia and elevated calcium × phosphate product, as well as severe bone resorption. All of these conditions set the stage for progression to severe metastatic and vascular calcification. At this stage, surgical parathyroidectomy is usually required, after which on going control of mineral metabolism is not easy to maintain.

Until recently it was thought that there was only one hormone secreted by the parathyroid gland, 1-84 PTH. For over 30 years it has been known that when serum calcium increased that the parathyroid gland responded by secreting fragment(s) of 1-84 PTH[2]. But, the biological role of those fragment(s) with regards to calcium

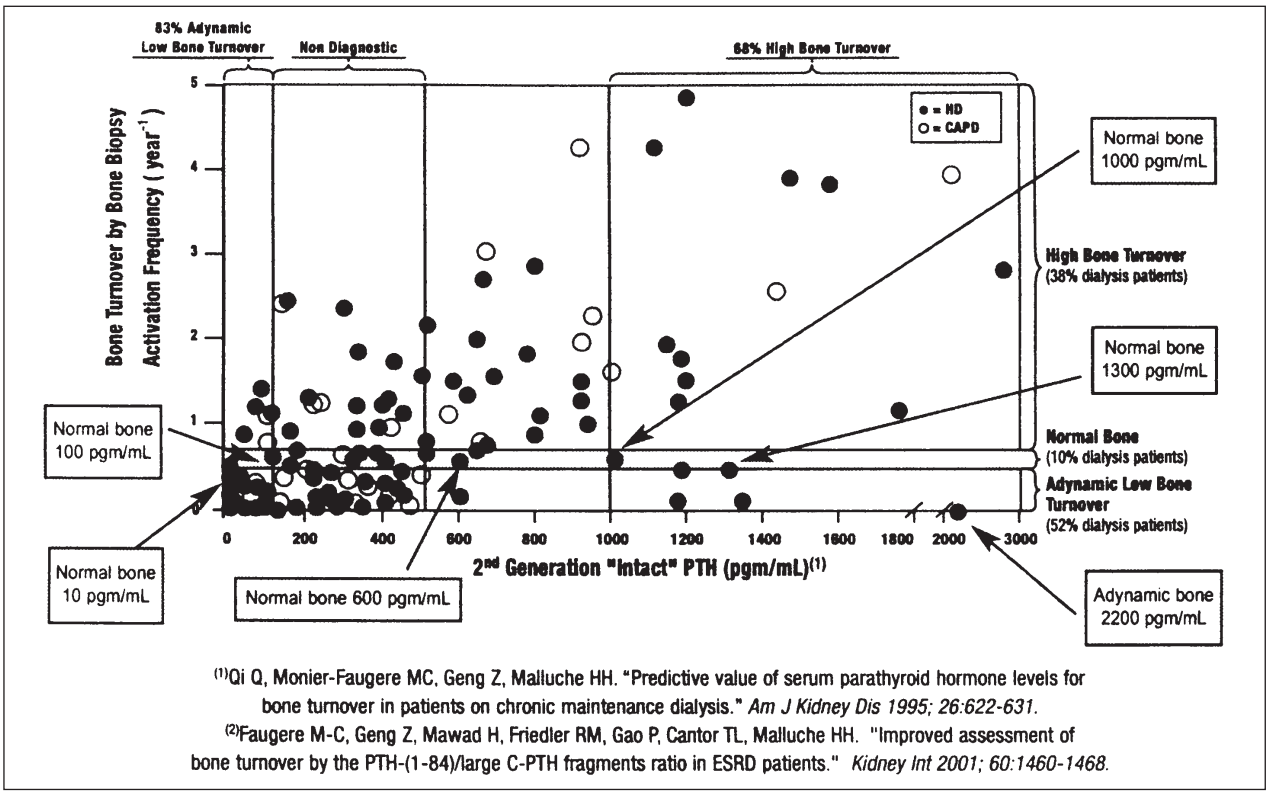

Fig. 1.—The relationship between 2nd generation «intact» PTH and bone turnover by bone biopsy.

metabolism was never known. But, our understanding improved when in 2000 Slatopolsky et al demonstrated that there is a large C terminal fragment(s) of 1-84 PTH (probably 7-84 PTH) that is secreted by the parathyroid gland and functions as a biological inhibitor of 1-84 PTH[3]. Working under the assumption that this fragment is 7-84 PTH synthetic 7-84 PTH was used to demonstrate a profound 1-84 PTH antagonistic effect on calcium metabolism. These hypocalcemic actions of the 7-84 PTH fragment has been demonstrated to rank 7-84 PTH as the most potent inhibitor of PTH yet described. 7-84 PTH has now been studied by several groups. Surprisingly, this 7-84 PTH has been demonstrated to bring about several dramatic inverse biological responses in comparison to 1-84 PTH, namely:

1. 7-84 PTH decreases bone resorption, whereas 1-84 PTH increases bone resorption[4].

2. 7-84 PTH decreases bone turnover to the point of causing adynamic low bone turnover disease, whereas 1-84 PTH increases bone turnover to the point of causing high bone turnover disease[5].

3. 7-84 PTH decreases serum calcium, whereas 1-84 PTH increases serum calcium[3,6].

4. 7-84 PTH does not stimulate adenylate cyclase (cyclase inactive PTH or CIP), whereas 1-84 PTH does stimulate adenylate cyclase (cyclase activating PTH or CAP)[3].

5. 7-84 PTH appears to operate through a C terminal PTH receptor, whereas 1-84 PTH operates through the PTH1R receptor[4].

Now, we understand that the parathyroid gland controls calcium metabolism by secreting two hormones with opposing potent biological activities. 1-84 PTH brings about an increase in serum calcium by increasing bone turnover and the excess of this 1-84 PTH results in high bone turnover disease. 7-84 PTH brings about a decrease in serum calcium by decreasing bone turnover and the excess of this 7-84 PTH results in adynamic low bone turnover disease. Therefore, a high value of a 1-84 PTH/7-84 PTH (or CAP/CIP) ratio indicates high bone turnover and a low value of a 1-84 PTH/7-84 PTH indicates a low bone turnover[8,9].

The ultimate goal of secondary hyperparathyroidism therapy has been to suppress the level of PTH into that target range where there is neither hypercalcemia nor high bone turnover disease (osteodystrophy) from inadequate suppression nor adynamic low bone turnover disease from oversuppression. Since the 1980's we have relied on the «intact» PTH assay to guide this

PTH suppressive therapy. However, we learned in 1998 that the term, «intact» as a description of the 2nd generation «intact» PTH assay was wrong, as the «intact» PTH assay measures the sum of the two hormones of the parathyroid gland, the 1-84 PTH agonist and the 7-84 PTH antagonist. With a 100% cross reactivity with 7-84 PTH any particular «intact» PTH patient assay value might be made up of as little as 10% 1-84 PTH/90% 7-84 PTH, or 90% 1-84 PTH/10% 7-84 PTH. This knowledge now has created problems as we can no longer refer to previous 2nd generation «intact» PTH assay values as simply PTH data. This non specificity of the «intact» PTH assay may provide an explanation for the alarming increase in the prevalence of adynamic low bone turnover disease. Indeed, an overestimating «intact» PTH assay could have easily resulted in over suppressive PTH therapy leading to adynamic low bone turnover disease[7].

The only accurate gold standard for evaluating a non invasive test like PTH for bone turnover is bone histomorphemetry. The problems with relying on the overestimating 2nd generation «intact» PTH assay can be seen in bone histomorphemetry. Bone biopsy studies have demonstrated that the «intact» PTH test is relatively non diagnostic of bone turnover with a mere 72% predictability. (see fig. 1) But, when bone histomorphemetry was used to evaluate the efficiency of the ratio of 1-84 PTH agonist/7-84 PTH inhibitor it was found to be diagnostic of bone turnover with a 93% predictability[8] (see fig. 2). These findings have been confirmed by Salusky and Goodman[9]. It has further been found that when the ionized calcium level in a dialysis patient is increased over a physiological range that this CAP/CIP ratio decreases in a linear manner. This finding is consistent with the understanding that the body when faced with hypercalcemia produces more of the 7-84 PTH and less of the 1-84 PTH (i.e., lower CAP/CIP ratio) to lower bone turnover and serum calcium and vice versa for hypocalcemia (i.e., higher CAP/CIP ratio).

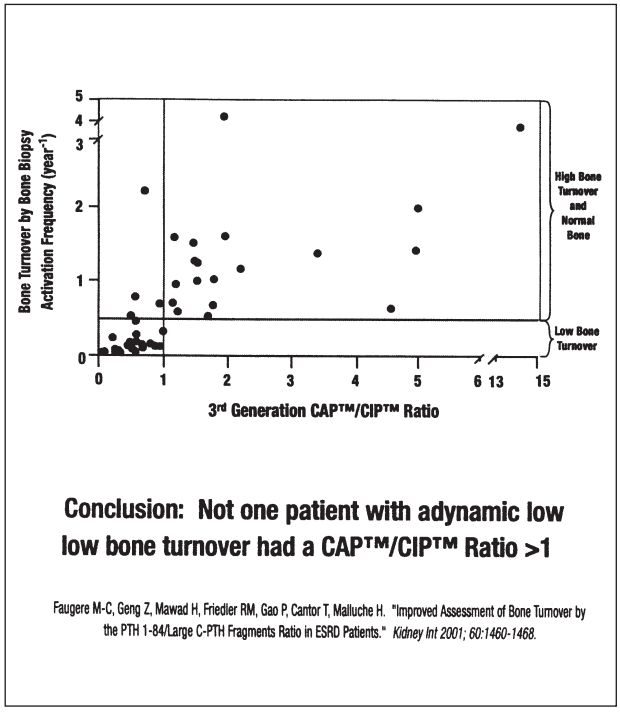

Fig. 2.—The relationship between the 3rd generation CAP™/CIP™ ratio and bone turnover by bone biopsy.

It is clear that over and under PTH suppressive therapies pose significant risks to the chronic kidney disease patient. As the patient is being managed for PTH, calcium, phosphate, vitamin D, calcium × phosphate product and bone quality an accurate PTH measurement is essential. With the elucidation of the role of the 7-84 PTH as an antagonist to 1-84 PTH and the improved accuracy of the CAP/CIP ratio for diagnosis of bone status, more bone histology studies are called for in order to establish appropriate ratio cutoffs under different therapeutic settings.

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