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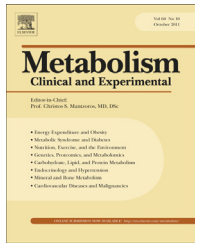

Comparison between a second and a third generation parathyroid hormone assay in hemodialysis patients

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ABSTRACT

Objective. Third generation parathyroid hormone (PTH) assays are new generation assays that do not recognize the $PTH_{7–84}$ fragment whereas second generation assays detect both $PTH_{1–84}$ and $PTH_{7–84}$ fragments. Despite the excellent correlation between both assays in chronic renal failure (CRF) subjects, the mean PTH levels are typically 50% lower with the third compared to the second generation assays. The assessment of third generation PTH assays has not been extensively studied in hemodialysis subjects. The purpose of our study was to compare a third generation PTH assay to a second generation one in a population of hemodialysis subjects.

Materials and methods. 92 haemodialysis subjects (36 women and 56 men) with a mean age of 67±12.9 years were included in this study. Anthropometric and clinical parameters (Body Mass Index (BMI) and blood pressure) were measured. Second and third generation PTH assays (Cis biomedical and Diasorin respectively) were performed in each subject. In addition, the following biochemical tests were measured: 25-hydroxyvitamin D (25-(OH)D), 1,25-hydroxyvitamin D ($1,25\text{-}(OH)_2D$), crosslaps and alkaline phosphatase.

Results. The mean second and third generation PTHs are respectively 211±205 pg/ml and 151±164 pg/ml. The mean third generation PTH values are 28.4% lower compared to the second generation ones. Both methods are strongly correlated ($r = 0.923$, $p < 0.001$). This correlation persisted without any significant difference after controlling for gender, age, BMI and Blood Pressure. However, the difference between both methods increases when baseline PTH increases. Each of the second and third generation method is significantly correlated with hemodialysis duration ($p < 0.01$), crosslaps ($p < 0.001$), alkaline phosphatase ($p < 0.05$), but not with age, BMI, Blood Pressure, 25-(OH)D or $1,25\text{-}(OH)_2D$ levels.

Conclusion. Our results show that both second and third generation PTH methods are strongly correlated in hemodialysis patients mainly when PTH values are low. However, the difference between both methods increases when PTH values are high. More research is needed to establish which method is the gold standard when PTH values are high.

Abbreviations: PTH, Parathyroid hormone; CRF, Chronic renal failure; 25-(OH)D, 25-hydroxyvitamin D; $1,25\text{-}(OH)_2D$, 1,25-hydroxyvitamin D; BMI, Body Mass Index; CKD, Chronic Kidney Disease.

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1. Introduction

Parathyroid hormone (PTH) has a critical role in skeletal and homeostatic regulation by its implication in bone remodelling. Osteitis fibrosa cystica, in which bone turnover is increased due to secondary hyperparathyroidism, is the main bone disease associated with Chronic Kidney Disease (CKD). This is why PTH measurement is used for the evaluation of CKD-mineral bone disease as an alternative to invasive bone biopsy [1]. PTH measurement also guided patient care since according to the Kidney disease: Improving Global Outcomes (KDIGO) guidelines, PTH levels should be maintained in the range of two to nine times the upper normal limit of the assay.

Among PTH measurement techniques, the first radioimmunological techniques were completely replaced by immunometric methods also named intact PTH with an improved specificity because they do not measure the C-terminal fragments. These immunoassays (commonly termed second-generation PTH immunoassays) use a pair of antibodies, a capture antibody directed against the (39–84) portion of the PTH molecule and a second antibody that recognizes the (13–24) portion of the peptide. They not only recognize $PTH_{1–84}$ but also cross-react to varying degrees with a family of large amino-truncated fragments, of which $PTH_{7–84}$ is the most abundant form [2]. $PTH_{7–84}$ antagonizes the $PTH_{1–84}$ and accumulates in patients suffering from CKD constituting 45% to 50% of the circulating PTH, thus explaining the PTH overestimation in secondary hyperparathyroidism due to chronic renal failure (CRF) [3]. More recently, a third generation of PTH immunoassay was developed. It is known as bioactive (or whole) PTH and it uses an anti-N-terminal antibody directed against the first four amino acids of PTH [4]. These immunoassays, therefore, do not measure the $PTH_{7–84}$ fragment. However, amino-PTH (N-PTH), a recently recognized form of PTH that is not truncated but modified by phosphorylation of a serine residue at position 17 [5], cross-reacts with these third-generation PTH assays but not with antibodies used in most second-generation immunoassays. The N-PTH also accumulates in CRF accounting for 15% of the circulating PTH.

Despite the recent (KDIGO) guidelines recommending PTH measurements in CRF management [1], there is a great variability in PTH hormone immunoassays results leading to the requirement for improving comparability in PTH results [6,7]. In addition, few studies compared second and third generation PTH assays [8–19]. These studies were performed in primary hyperparathyroidism [8,9] or secondary hyperparathyroidism [10–19]. Despite an excellent correlation between both methods in CRF, the mean PTH levels are typically 50% lower with the bioactive assays compared to second generation PTH assays [2,4,17,18]. In the CHOICE study, the bioactive PTH constitutes 53% of the intact PTH (interval 25%–89%) [14]. Recently, the first new chemiluminescent third generation PTH was automated on the LIAISON automate. To our knowledge, no previous studies analyzed this assay in hemodialysis subjects.

The purpose of our cross-sectional study was to compare both PTH methods in hemodialysis subjects and to look at the relation between each method and the anthropometric, clinical, biological and therapeutic parameters.

2. Materials and methods

2.1. Subjects

The population was composed of 92 hemodialysis patients from the hemodialysis unit of our hospital. Subjects were hemodialysed 2 or 3 times weekly. The mean duration from the time of dialysis initiation was 4.67 ± 4.4 years. The following anthropometric parameters were measured: age (years), weight (kg) height (cm). Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Fifty patients (54.3%) were treated with alfacalcidol, 31 (32.6%) with sevelamer and 56 (60.9%) with calcium carbonate. Only one patient was treated by cholecalciferol. The posology of these medications was registered.

2.2. Biological parameters

Predialysis blood samples were withdrawn and immediately centrifuged. The following biological parameters were assayed on the same day on the Vitros automate on dry chemistry (Johnson and Johnson, Orthoclinical, Strasbourg, France): alkaline phosphatase, creatinine, calcium, phosphorus and albumin. Corrected calcium was calculated according to the formula: corrected calcium = total calcium + 0.02 × (40 – albumin in g/l). Measurements of PTH, 25-(OH)D, 1,25-$(OH)_2$D and crosslaps were delayed and measured on serum tubes previously frozen at minus 80 °C.

Second generation PTH was measured using the immunoradiometric ELSA-PTH (Cis, France). This assay uses a monoclonal antibody specific for the central and C terminal part of the molecule (amino acids 39–84) and a second polyclonal antibody recognizing the N terminal part of the PTH (amino acids 1–34). It recognizes both the PTH 1–84 and the peptide 7–84. The intra and inter-assay coefficients of variation are respectively below 7% and 8%. The lower limit of detection is 0.7 pg/ml and the measurement range is between 0.7 and 1500 pg/ml. The third generation PTH was measured with the chemiluminescent Diasorin assay on the Liaison automate (Stillwater, USA) an assay that allows the determination of the PTH 1–84 without cross-reactivity with the $PTH_{7–84}$ fragment. The assay uses two polyclonal antibodies the first one specific to the N-terminal extremity of the peptide and the second specific to the C-terminal part ensuring 100% specificity for the whole PTH molecule. The minimal detectable level is 1.7 pg/mL. The inter-assay coefficient of variation is below 10 %, the measurement range is between 4 and 1800 pg/ml. The respective normal values for healthy subjects are 7 to 36 pg/ml for the third generation assay and 11 to 62 pg/ml for the second generation assay. Each PTH method (third and second generation) is a representative method of PTH measurement. 1,25-$(OH)_2$D was measured by a radioimmunological assay Diasorin (Stillwater, USA). The reference values for normal subjects are between 25.1 and 66.1 pg/mL whereas for CRF subjects values are between 1.6 and 17.3 pg/mL. 25-(OH)D was measured using the Diasorin chemiluminescent automate Liaison (Stillwater, USA). Finally, crosslaps were measured using the Elecsys automate (Roche Diagnostics, Mannheim,