

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

HIPERPARATIREOIDISMO SECUNDÁRIO À HIPOVITAMINOSE D
DEPENDE DOS NÍVEIS SÉRICOS DE MAGNÉSIO

TESE DE MESTRADO

TIAGO SCHUCH

Porto Alegre, janeiro de 2010

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SUMÁRIO

Lista de Tabelas e Figuras	iv
Lista de Abreviaturas	v
Resumo	vi
Introdução	vii

Artigo

Hiperparatireoidismo secundário à hipovitaminose D depende dos níveis séricos de magnésio

Resumo	12
Introdução	13
Pacientes e métodos	15
Participantes do estudo	15
Análise bioquímica	16
Análise estatística	16
Resultados	17
Status da vitamina D	17
Hiperparatireoidismo secundário	17
Discussão	18
Referências Bibliográficas	22
Perspectivas futuras	30

LISTA DE TABELAS E FIGURAS

Artigo

Tabela 1.	Características clínicas e laboratoriais dos pacientes de acordo com o status de vitamina D	27
Tabela 2.	Características clínicas e laboratoriais dos pacientes com ou sem hiperparatireoidismo secundário	28
Figura 1.	Concentrações de PTH de acordo com os níveis de 25-OHD. Painel A: todos pacientes (n=91); Painel B: pacientes com magnésio sérico > 2,1mg/dl (n=40).....	29

LISTA DE ABREVIATURAS

eGFR	<i>Estimated glomerular filtration rate</i>
Mg	<i>Magnesium</i>
PTH	<i>Parathyroid hormone</i>
25-OHD	<i>25-hydroxivitamin D</i>

Resumo

Contexto. A deficiência de vitamina D em adultos pode precipitar ou agravar osteopenia e osteoporose, causar fraqueza muscular e osteomalácia, e aumentar o risco de fraturas ósseas. Alguns destes efeitos podem ser mediados pelo hiperparatireoidismo secundário a níveis diminuídos de 25-hidroxivitamina D (25-OHD). Não está claro porque alguns indivíduos não desenvolvem elevação dos níveis de hormônio da paratireóide (PTH) em consequência à deficiência de vitamina D.

Objetivos. Estimar a prevalência de hipovitaminose D e hiperparatireoidismo secundário em uma amostra de pacientes adultos ambulatoriais, e analisar possíveis causas de ausência de correlação entre os níveis de 25-OHD e PTH.

Delineamento e cenário. Estudo transversal de 91 pacientes ambulatoriais de um centro de atenção terciária no sul do Brasil (latitude 30° sul).

Pacientes. Adultos a partir de 40 anos de idade.

Desfechos principais. Níveis séricos de 25-OHD medidos por quimioluminescência e níveis de PTH medidos por eletroquimioluminescência.

Resultados. Idade média foi $60,3 \pm 12$ anos, 56 (61,5%) eram mulheres, e 70 (76,9%) eram brancos. Hipovitaminose D foi encontrada em 69 (75,9%), 11 (12,1%) tinham hiperparatireoidismo secundário e nenhum tinha hipomagnesemia ($Mg < 1,5$ mg/dl). Não houve correlação significativa entre os níveis de 25-OHD e PTH, porém esta correlação tornou-se significativa quando apenas indivíduos com níveis de magnésio acima de 2,1 mg/dl foram considerados na análise ($r = 0,37$, $p = 0,02$). Houve correlação positiva entre os níveis de PTH e magnésio na faixa normal ($r = 0,29$, $p < 0,01$).

Conclusões. A associação entre hipovitaminose D e hiperparatireoidismo secundário é dependente dos níveis séricos de magnésio.

INTRODUÇÃO

A vitamina D desempenha um papel importante na saúde humana, com funções que estendem-se além dos seus bem conhecidos efeitos sobre o metabolismo mineral e ósseo, como função muscular, diferenciação celular, e imunidade (1). Níveis inadequados deste hormônio parecem ser achado comum na população adulta de todo o mundo, apesar de diferenças na prevalência de hipovitaminose D em relação à idade, grupo étnico, latitude, estação do ano, quantidade de exposição solar, fortificação alimentar ou uso de suplementos de vitamina D (2,3). A hipovitaminose D pode causar hiperparatireoidismo secundário, precipitar ou agravar osteopenia e osteoporose, causar osteomalácia e fraqueza muscular, aumentar o risco de quedas e fraturas ósseas (4), e tem sido associada ao desenvolvimento de câncer (5), diabetes (6), e doenças autoimunes (7). Uma vez que a deficiência de vitamina D pode ser corrigida facilmente e por meios seguros e baratos, tem sido dada atenção aumentada para identificar e corrigir este problema de saúde (8).

O método padrão para avaliação do status de vitamina D é a medida dos níveis séricos de seu principal metabólito, 25-hidroxivitamina D (25-OHD) (9), devido à sua meia-vida longa, correlação com a absorção de cálcio, e porque a etapa de 25-hidroxilação não é regulada. Entretanto, há considerável variação e falta de padronização entre os diferentes ensaios utilizados para sua dosagem (10-11).

A hipovitaminose D é associada ao desenvolvimento de hiperparatireoidismo secundário, quando os níveis de PTH estão relativamente elevados para a concentração de cálcio associada, apesar destes ainda poderem estar no intervalo de referência (1). Baseado na correlação inversa entre os níveis séricos de 25-OHD e PTH, alguns experts sugerem que os níveis adequados de vitamina D para supressão do PTH deveriam ser de pelo menos 30ng/ml, apesar de

ainda não haver consenso (12-14). Não obstante, alguns pacientes com hipovitaminose D não apresentam níveis elevados de PTH, uma condição descrita como hipoparatiroidismo funcional (15), a qual não é rara (1,16). Estes pacientes parecem ter menos conseqüências sobre a saúde do que aqueles com hiperparatiroidismo secundário, como níveis elevados de marcadores de remodelamento ósseo e aumento do risco de mortalidade (15,17,18). As causas desta condição ainda não estão claras. Um estudo relatou depleção de magnésio em todos pacientes diagnosticados com hipoparatiroidismo funcional (19), e em outros esta condição tem sido também associada à hipoalbuminemia (20), uso de diuréticos tiazídicos (21), e a um índice de massa corporal aumentado (22).

O objetivo deste estudo foi avaliar a prevalência de hipovitaminose D e hiperparatiroidismo secundário em pacientes ambulatoriais adultos do sul do Brasil (latitude 30⁰), e identificar fatores associados envolvidos na resposta do PTH à hipovitaminose D.

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ARTIGO

Hyperparathyroidism secondary to hypovitaminosis D depends on serum levels of magnesium

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Abstract

Context. Vitamin D deficiency in adults may precipitate or worsen osteopenia and osteoporosis, cause muscular weakness and osteomalacia, and increase the risk of bone fractures. Some of these effects may be mediated by secondary hyperparathyroidism induced by low 25-hydroxyvitamin D (25-OHD) levels. It is not clear why some individuals do not develop elevation in parathyroid hormone (PTH) levels following vitamin D deficiency.

Objective. To estimate the prevalence of hypovitaminosis D and secondary hyperparathyroidism in a sample of adult ambulatory patients, and analyze possible causes of absence of correlation between 25-OHD and PTH levels.

Design and setting. Cross-sectional study of 91 outpatients of a tertiary care center in Southern Brazil (latitude 30°S).

Patients. Adults aged 40 years or older.

Main Outcome Measures. Serum levels 25-OHD measured by chemiluminescence and serum levels of PTH measured by electrochemiluminescence.

Results. Mean age was 60.3 ± 12 years, 56 (61.5%) women, and 70 (76.9%) white. Hypovitaminosis D was found in 69 (75.9%), 11 (12.1%) had secondary hyperparathyroidism and none had hypomagnesemia ($\text{Mg} < 1.5 \text{ mEq/L}$). There was no significant correlation between serum levels of 25-OHD and PTH, but this correlation became significant when individuals with magnesium serum level $> 2.1 \text{ mg/dl}$ were considered in the analysis ($r = 0.37$, $p = 0.02$). There was a positive correlation between PTH and serum magnesium levels in the normal range ($r = 0.29$, $p < 0.01$).

Conclusions. The association between hypovitaminosis D and secondary hyperparathyroidism is dependent on serum levels of magnesium.

Introduction

Vitamin D has a major role in human health, with functions that extend beyond its well known effects over mineral and bone metabolism, such as muscle function, cellular differentiation, and immunity (1). Inadequate levels of this hormone seems to be a common finding in the adult population throughout the world, despite differences in prevalence regarding to age, ethnicity, latitude, season, amount of sun exposure, vitamin D supplementation or food fortification (2,3). Hypovitaminosis D may cause secondary hyperparathyroidism, precipitate or worsen osteopenia and osteoporosis, cause osteomalacia and muscle weakness, increase the risk of falls and bone fracture (4), and it is been associated with development of cancer (5), diabetes (6), and autoimmune diseases (7). Since vitamin D deficiency can be corrected by easy, safe, and inexpensive means, increased attention has been given to identify and correct this health issue (8).

The standard method for evaluation of vitamin D status is the measurement of serum levels of its main metabolite, 25-hydroxyvitamin D (25-OHD) (9), because of its long serum half life, correlation with calcium absorption, and the 25-hydroxylation step is unregulated, even though there is considerable variation and lack of standardization between different assays (10-11).

Hypovitaminosis D is associated to development of secondary Hyperparathyroidism, when PTH levels are relatively elevated for the associated serum calcium concentration, although it may be still in the reference range (1). Based on the inverse correlation between serum levels of 25-OHD and parathyroid hormone (PTH), some experts suggest that this should be at least 30 ng/ml, although there is still no consensus (12-14). However, some patients with hypovitaminosis D do not show elevated PTH levels, a condition described as functional hypoparathyroidism (15). Functional hypoparathyroidism is not uncommon (1,16),

and these patients seem to have less health consequences than those with secondary hyperparathyroidism, such as elevated bone remodeling markers and increased mortality risk (15,17,18). Causes of this condition are still unclear. One study reported magnesium depletion in all patients diagnosed with functional hypoparathyroidism (19), and in others PTH concentrations have also been associated with hypoalbuminemia (20), thiazide diuretic use (21), and body mass index (22).

The aim of this study was to evaluate the prevalence of hypovitaminosis D and secondary hyperparathyroidism in adult ambulatory patients in Southern Brazil (latitude 30⁰) and to identify associated factors implied in parathyroid hormone response to hypovitaminosis D.

Patients and methods

Study participants: consecutive ambulatory patients sent between April and May/2008 (early autumn) for blood collection by their assistant physician to the laboratory area of Hospital de Clinicas de Porto Alegre were enrolled in the study. Inclusion criterion was age ≥ 40 years old. Exclusion criteria were: inability to walk, vegetarian or lactovegetarian feeding habit, alcohol or illicit drugs abuse, renal or hepatic failure, chronic diarrhea, history of previous gastrointestinal surgery, and hypercalcemia. Renal failure was defined as a serum creatinine above 1.5 mg/dl. The study protocol was approved by the Institucional Ethics in Research Committee and individuals gave written informed consent. Eligible patients were instructed to fill a standardized questionnaire about lifestyle and medical history, containing data about age, smoking status, alcohol use or illicit drug abuse, ethnicity, physical activity levels (graded according to ref. 23), use of sunscreen blockers or drugs known to affect mineral metabolism (calcium and vitamin D supplements, thiazide diuretics, bisphosphonates, glucocorticoids, anticonvulsivants and rifampicine). Two additional blood samples for the

study were collected, at the same time of the blood collection ordered by their attending physicians.

Biochemical analysis

25-OHD was measured by chemiluminescence (LIAISON® kit, DiaSorin Inc., Stillwater, MN-USA) – intra-assay CV 8-13% and interassay CV 8-15%. PTH was measured by electrochemiluminescence (Elecsys-Modular E-170, Roche Diagnostics, Indianapolis-USA) – intra-assay CV 0.6-1.8% and interassay CV 1.6-3.4%. Serum calcium, albumin, magnesium and creatinine were measured by standard routine methods (Modular-P, Roche Diagnostics, Indianapolis-USA). All blood samples were collected in the morning. Samples for 25-OHD were kept frozen at -70°C for a single time testing. The other tests were performed from a separate sample processed within the first hour after specimen collection. The equation of MDRD (Modification of Diet in Renal Disease) was used for calculation of the estimated glomerular filtration rate (eGFR) (24). Hypovitaminosis D was defined as serum 25-OHD levels below 30 ng/ml. Secondary hyperparathyroidism was defined as PTH levels above 65 pg/ml (the upper limit of the reference range).

Statistical methods

Results are expressed in mean \pm standard deviation. Comparisons between variables were made by t-student test and one-way ANOVA for continuous variables with normal distribution, and by chi-squared test for categorical variables. Correlations between two continuous variables were determined by Pearson's correlation coefficient. Multivariate analyses were done by multiple linear regression analysis (stepwise) with endpoints considered as dependent variables. Statistical analysis were made using the 13th version of the Statistical Package for Social Sciences (SPSS). Analysis with an α error $\leq 5\%$ were considered as statistically significant.

Results

A total of 97 patients were screened, and 6 patients were excluded due to creatinine levels above 1.5 mg/dl. Therefore, 91 patients were analyzed. The mean age was 60.3 ± 12 years, 56 (61.5%) were women, and 70 (76.9%) were white.

Vitamin D status

Hypovitaminosis D was observed in 69 (75.9%) patients. Clinical and laboratory features of patients with and without hypovitaminosis D are shown in table 1.

Patients with hypovitaminosis D were older ($P = 0.04$), and had a lower level of physical activity ($P = 0.01$) than those with adequate levels of this hormone. There were no significant differences between groups regarding to gender, ethnicity, sunscreen use, calcium or vitamin D supplement use, thiazide diuretic, bisphosphonate or glucocorticoid use. Also, no significant differences were found regarding to mean serum levels of PTH, calcium, albumin, magnesium and creatinine, and eGFR.

There were no significant correlations between serum levels of 25-OHD and calcium ($r = -0.16$; $P = 0.12$), albumin ($r = 0.04$; $P = 0.69$), magnesium ($r = -0.04$; $P = 0.74$), creatinine ($r = 0.09$; $P = 0.42$), and eGFR ($r = -0.04$; $P = 0.68$).

Secondary hyperparathyroidism

PTH levels above 65 pg/ml were found in 11 (12.1%) patients. Of those, 8 (72.7%) had hypovitaminosis D. Clinical and laboratory features of patients with and without secondary hyperparathyroidism are shown in table 2.

Patients with secondary hyperparathyroidism were older ($P = 0.04$), did not use sunscreen ($P = 0.03$), and as expected had higher serum levels of creatinine ($P < 0.01$), with consequently lower eGFR ($P < 0.01$) than patients without secondary hyperparathyroidism. There were no significant differences between groups regarding to gender, ethnicity, physical

activity levels, calcium or vitamin D supplement use, thiazide diuretic, bisphosphonate, or glucocorticoid use. Also, no significant differences were found regarding to mean serum levels of 25-OHD, calcium, albumin or magnesium.

There was no correlation between serum levels of 25-OHD and PTH ($r = 0.10$; $P = 0.35$). However, that correlation reached significance when only patients in the upper quartile of magnesium levels (above 2.1 mg/dl) were considered in the analysis ($r = 0.37$; $P = 0.02$; $n = 40$) (Figure 1.). Also, serum levels of PTH were correlated with age ($r = 0.32$; $P = 0.02$), creatinine ($r = 0.382$; $P < 0.01$), eGFR ($r = -0.379$; $P < 0.01$), and magnesium levels ($r = 0.29$; $P = 0.01$). No correlation was found between PTH and calcium ($r = 0.02$; $P = 0.85$) or albumin ($r = 0.19$; $P = 0.08$).

In multivariate linear regression analysis of all patients, with serum levels of PTH as the dependent variable and age, eGFR, serum levels of 25-OHD and magnesium as independent variables, only eGFR (adjusted R^2 : 0.15; β coefficient: -0.39; $P < 0.01$) and magnesium (adjusted R^2 : 0.22; β coefficient: 0.28; $P < 0.01$) remained significantly associated with PTH. Considering only patients with serum levels of magnesium > 2.1 mg/dl ($n=40$), the variation of PTH was significantly associated with magnesium (adjusted R^2 : 0.14; β coefficient: 0.36; $P = 0.01$), eGFR (adjusted R^2 : 0.25; β coefficient: -0.33; $P = 0.02$), and 25-OHD (adjusted R^2 : 0.31; β coefficient: -0.28; $P = 0.04$).

Discussion

In this sample of adult outpatients from Southern region from Brazil, hypovitaminosis D was observed in approximately 76%, especially in older and sedentary patients. Notwithstanding, we found a low prevalence (12%) of secondary hyperparathyroidism, which was not expected. Also, we didn't find correlation between serum 25-OHD and PTH levels, unless we considered only patients in the upper quartile of magnesium concentrations.

Global estimates of vitamin D have found large differences in the prevalence of vitamin D inadequacy around the world, depending on different cutoff points and laboratory methods used for dosing 25-OHD and defining vitamin D status (3). As an example, in a review study by Holick M., 40 to 100% of community living elderly from U.S. and Europe were vitamin D deficient (4). Previous reports from Brazil found prevalence rates of vitamin D inadequacy in postmenopausal women ranging from 42.4 to 66.7% using the serum 25-OHD level cutoff point of 30 ng/ml (25,26), and in 57.3% of community living elderly, using the cutoff point of 20 ng/ml (27). The higher latitude of Porto Alegre in relation to the other cities in Brazil where previous studies were conducted could have accounted for the higher prevalence rate of hypovitaminosis D observed.

Another factor that could be attributed to the differences in the hypovitaminosis D rates is that different methods are used for dosing 25-OHD. In fact, one study (26) mentioned above used the Nichols ADVANTAGE assay, which showed a poor correlation with the gold-standard method of chromatography-tandem mass spectrometry (LC-MS/MS) (28). However, the method used in this study was previously shown to have acceptable correlation with the DiaSorin RIA method (25), and also with the LC-MS/MS method (28,29). In fact, a study using LC-MS/MS as the method of reference for dosing serum levels of 25-OHD reported a hypovitaminosis D prevalence of 71.1% in elderly men living in U.S. communities (mean age 73.8 years), similarly to our findings (8).

We observed a low rate of secondary hyperparathyroidism in spite of a high rate of vitamin D inadequacy. Very few studies have specifically addressed this issue, and the prevalence of this condition is still undefined, being described to be up to 75% (17). It is clinically relevant to identify patients with functional hyperparathyroidism, since they seem to have more favorable outcomes when compared to patients that develop secondary

hyperparathyroidism (15,17-19,30). One report, on a cohort of 1280 elderly men and women living in residential care facilities, found elevation in bone remodeling markers (PINP and CTX-I) and increased mortality risk only in patients with hypovitaminosis D and elevated PTH levels (17). Another authors, evaluating postmenopausal women with vertebral fractures, found increased bone turnover markers only in those with hypovitaminosis D and secondary hyperparathyroidism (15). Moreover, the Fracture Risk Epidemiology in the Frail Elderly (FREE) Study reported increased mortality in frail elderly patients with elevated PTH and high bone turnover independent of vitamin D status (18,30). We identified a magnesium dependency over the elevation of serum PTH following hypovitaminosis D, as the correlation between serum 25-OHD and PTH became significant only when patients in the upper quartile of magnesium levels were included in statistical analysis. To our knowledge, only one study had described similar findings. Sahota et al. reported, in a small group of 10 patients with functional hypoparathyroidism, that all of them had magnesium deficiency when evaluated by a magnesium loading test, and still, those showed a significant elevation in PTH and bone turnover markers after oral magnesium supplementation (19).

Possible limitations of this study include small sample size, which could have blunted the correlation between 25-OHD and variables such as gender, sunscreen use and ethnicity, as reported in previous studies. Also, we are aware that magnesium status may be better stated through a magnesium load/retention test, but the finding that serum magnesium levels in the normal range influence the serum PTH response to hypovitaminosis D is a new interesting aspect that should be properly addressed in future studies.

In conclusion, hypovitaminosis D is highly prevalent, and in a significant proportion of patients this is not coupled to secondary hyperparathyroidism. To our knowledge, the

correlation between serum magnesium levels in the normal range and PTH in a population of vitamin D inadequacy has not been previously reported.

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Table 1. Clinical and laboratory features of patients according to vitamin D status

	Vitamin D status		P
	Hypovitaminosis D	Adequate	
	69 (75.8)	22 (24.2)	
Age (years)	60.6 ± 12.3	59.6 ± 11.5	0.04
Women	46 (66.6)	10 (45.5)	0.07
White	53 (76.8)	17 (77.3)	0.96
Physical activity			
None / mild	62 (92.5)	16 (72.7)	0.01
Moderate / intense	5 (7.5)	6 (27.2)	
Sunscreen use	21 (30.4)	4 (18.2)	0.26
Vit. D supplement	7 (10.1)	4 (18.2)	0.31
Calcium supplement	10 (14.5)	5 (22.7)	0.37
Thiazide diuretic	23 (33.3)	11 (50)	0.16
Bisphosphonate	5 (7.2)	1 (4.5)	0.66
Glucocorticoid	1 (1.4)	1 (4.5)	0.39
PTH (pg/ml)	44.2 ± 17.2	44.2 ± 15.7	0.99
Total calcium (mg/dl)	9.1 ± 0.5	9 ± 0.4	0.21
Albumin (g/L)	4.4 ± 0.3	4.4 ± 0.3	0.7
Magnesium (mg/dl)	2.1 ± 0.2	2.1 ± 0.2	0.97
Creatinine (mg/dl)	0.8± 0.2	0.9 ± 0.2	0.16
eGFR	89.5 ± 22.1	85.3 ± 21.1	0.44
25-OHD (ng/ml)	18.6 ± 5.8	38.4 ± 7.9	---

Table 2. Clinical and biochemical features of patients with or without secondary hyperparathyroidism

	Secondary hyperparathyroidism		P
	Present	Absent	
	11 (12.1)	80 (87.9)	
Age (years)	67.3 ± 9.1	59.4 ± 12.1	0.04
Women	5 (45.5)	51 (63.8)	0.24
Whites	6 (54.5)	64 (80)	0.06
Physical activity			
None / mild	8 (72.7)	44 (56.4)	0.30
Moderate / intense	3 (27.3)	34 (43.6)	
Sunscreen use	0	25 (31.3)	0.03
Vit. D supplement	1 (9.1)	10 (12.5)	0.74
Calcium supplement	1 (9.1)	14 (17.5)	0.48
Thiazide diuretic	4 (36.4)	30 (37.5)	0.94
Bisphosphonate	1 (9.1)	5 (6.3)	0.72
Glucocorticoids	1 (9.1)	1 (1.3)	0.09
25-OHD (ng/ml)	22.0 ± 9.8	23.5 ± 10.7	0.67
Total calcium (mg/dl)	9.1 ± 0.4	9.1 ± 0.4	0.51
Albumin (g/L)	4.4 ± 0.3	4.3 ± 0.2	0.31
Magnesium (mg/dl)	2.2 ± 0.3	2.1 ± 0.2	0.12
Creatinine (mg/dl)	1.1 ± 0.2	0.8 ± 0.2	< 0.01
eGFR	65.3 ± 19.1	91.6 ± 20.3	< 0.01
PTH (pg/ml)	77.7 ± 9.1	39.6 ± 11.5	---

Figure 1. PTH concentrations according to 25-OHD levels. Panel A: all patients (n=91);
Panel B: patients with serum magnesium > 2.1mg/dl (n = 40)

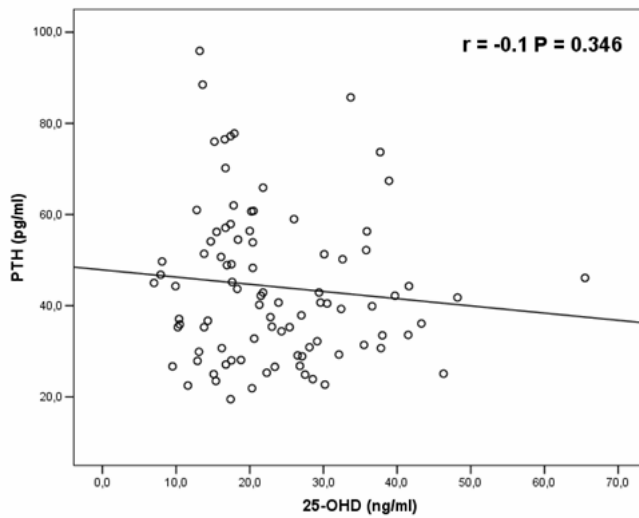


Figure 1a. PTH concentrations according to 25-OHD levels in all patients (n=91)

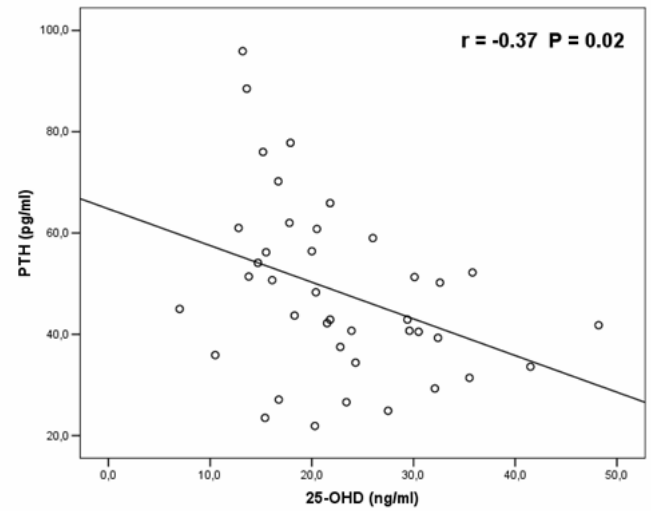


Figure 1b. PTH concentrations according to 25-OHD levels in patients with serum magnesium > 2.1 mg/dl (n=40)

PERSPECTIVAS FUTURAS

Como seguimento da linha de pesquisa em vitamina D e hiperparatireoidismo secundário, pretendemos estudar o efeito da sazonalidade sobre os níveis de vitamina D e PTH, bem como avaliar as relações entre magnésio, PTH e vitamina D através do teste de sobrecarga/retenção de magnésio e através da reposição oral deste eletrólito.

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