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VITAMIN D DEFICIENCY AND INSUFFICIENCY LEVELS IN PATIENTS ATTENDED AT A HEALTHCARE TEACHING-HOSPITAL LABORATORY

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ABSTRACT

Aim: Characterize the Vitamin D serum profile, by means of exams done in patients, from 2012 to 2016, in a healthcare Teaching-Hospital laboratory, correlating it with gender, age range, and health care systems types-Public or Private. **Material and Methods:** Retrospective, registry-scan study using reports of 44,700 Vitamin D serum dosages dosages carried out in patients in routine consultations, from the age of two. **Results:** Female patients done 36,654 (82%) Vitamin D exams and male 8,046 (18%) exams. By the Public system 24,965 (55.8%) exams were performed and 19,735 (44.2%) by the Private system ($p<0.005$).Male patients' age in the Public system varied from 5 to 94 years and for the Private system, it varied from 2 to 75 years ($p<0.005$).Female patients' age in Public system varied from 12 to 97 years and for the Private, it varied from 3 to 86 years ($p<0.005$).The age ranges with the highest number of requests were adult (43%) and elderly (33%).Levels of Vitamin D Deficiency and Insufficiency were found in all age levels (30.5%) except for infancy ($p<0.005$). **Conclusion:** Vitamin D Deficiency and Insufficiency levels were found, in both genders, in all age ranges, except for infancy, but with predominance in the Private system and in female gender.

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INTRODUCTION

Although defined as fat soluble, Vitamin D is conceptually a pro-hormone (secosteroid) which plays a fundamental role in calcium homeostasis and bone metabolism. Vitamin D food sources are not able to supply the needs of this vitamin. Breast milk, although being the best food to new-born and infant babies, has low concentrations of Vitamin D, even if the nursing mother is sufficient in Vitamin D (Masvidal *et al.*, 2012; Peppelenbosch *et al.*, 2017). Vitamin D deficiency is one of the most frequent nutrition disorders across the world (Manson *et al.*, 2016). In our country, despite the fact that most the population live in regions of adequate sun exposure, hypovitaminosis D is a common problem not restricted only to the elderly or menopaused women, but also affecting children and adolescents (Oliveira *et al.*, 2014). Epidemiological studies point to extra skeletal actions of Vitamin D, suggesting that its deficiency may be associated not only to rickets in children and osteomalacia and osteoporosis in adults, but also to the risk of fractures, muscular weakness, psoriasis, depression and some neoplasms (Cianferotti *et al.*, 2017; Kočovská *et al.*, 2017; Yang *et al.*, 2017). Determining the epidemiological distribution of this deficiency is fundamental towards promoting the right control and prevention strategies, being of prime importance the use of clinical and biochemical indicators related to vitamin deficiency (Alves *et al.*, 2016). Thus the present study aims to characterize the Vitamin D serum profile, based on appraisals of laboratory exams carried out in patients from 2012 to 2016, in the laboratory of clinical analysis of a Teaching-Hospital correlating it with gender, age range, types of health care systems - Private or Public, in order to know the local serum reality of this micronutrient.

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MATERIAL AND METHODS

This retrospective study characterized the vitamin D serum profile based on registry-scan of laboratory exams carried out in patients, of both genders, in the clinical analysis laboratory in a Teaching Hospital, from 2012 to 2016. The Teaching-Hospital data bank system, for being electronic via, allowed direct filtering of the criteria to be analyzed, automatically excluding serum dosages of pregnant women, hospitalized

patients suffering from chronic diseases, transplanted patients, institutionalized or making use of vitamin supplementation. The following data were collected: gender, age at the lab exam collecting time, exams carried out by Public or Private health care system. The age range was classified according to preconized growth phases: infancy (2 to 10 years); adolescence (11 to 17 years), young adult (18 to 40 years), adult (41 go 65 years) and elderly (>65 years) (Elderly Statute, 2003; WHO, 2013). In the Teaching-Hospital clinical analysis laboratory, Vitamin D is identified by the High Performance Liquid Chromatography method, with the following reference values: Deficiency <20.0 ng/mL; Insufficiency 20.0-29.9 ng/mL; Sufficiency ≥30.0 ng/mL. The study was approved by the local ethics committee (Report # 2, 131, 310/2017), and for being a laboratory registry-scan study the informed consent was not applied.

Statistical Analysis

The results were previously subjected to descriptive statistics to determine normality. The Mann-Whitney test was used for independent samples with non-normal distribution and the Student t test was used for samples with normal distribution. The Chi-square (χ^2) or Fisher exact tests were used for comparison between variables. Significance level was established in 5%. The results were expressed in percentages (%), Mean (M) and Standard Deviation (SD). The statistical tests were performed using the GraphPad Instat program 3.0 version, GraphPad Software Inc. San Diego, California USA, www.graphpad.com.

RESULTS

In a five-year period (2012-2016), 44,700 exams were requested and performed to assess Vitamin D serum levels, in a Teaching-Hospital laboratory. From this total 36,654 (82%) exams were done by female patients and 8,046 (18%) by male patients and, in relation to health care systems, 24,965 (55.8%) exams were carried bout by the Public system and 19,735 (44.2%) by Private system. The difference between the number of patients of both genders and types of health care system was significant (Fisher Exact Test; $p<0.005$). Figure 1 presents the distribution of Vitamin D reference serum levels (Deficiency, Insufficiency, Sufficiency), obtained after analyzing the exams carried out by the 44,700 patients, according to age range. The total prevalence of Sufficiency has been found in 69.5% of cases, Insufficiency in 24.5% and Deficiency in 6% of cases, after the analysis of exams carried out. The age ranges with the highest number of serum dosages were adult (43%) and elderly (33%). Deficiency and Insufficiency levels of Vitamin D were found in all age ranges, except for infancy, totaling 30.5% being these differences statiscally significant (χ^2=807.33; $p<0.005$). (Figure 1). The data, presented as follows, have been conducted for a better comparative analysis of gender by health care systems, age range and serum levels. Thus, the number (N) distribution of male and female patients, from Public and Private system, in relation to age range, is demonstrated, respectively, on Tables 1 and 2. There has been a higher prevalence of male patients from Public (62%), but despite the fact that a high number of patients, who did the exam, were in the elderly age range (~42%) among the others evaluated and, in the Private system, the highest prevalence were for adult and young adult ranges, totaling approximately 26%, meaning, therefore, a higher number of dosages in these referred age ranges, highlighting significant difference between these variables (χ^2=1906.0; $p<0.005$) (Table 1). Age for Public male patients varied from 5 to 94 years (M=62.77 years; SD±19.9; CI95%=58.18-67.35) and for the Private system; it varied from 2 to 75 years (M=42.28 years, SD±20.5, CI95%=36.20-48.36), being this difference statistically significant ($p<0.005$). There has been higher prevalence for Public female patients (54.5%), but despite the fact that a high number of patients, who did the exam, were in adult and elderly ranges, totaling approximately 51%. In the Private system, the highest prevalence were for adult and young adult ranges, totaling about 37%, meaning, therefore, a higher dosage numbers in such age ranges, with significant difference between these variables (χ^2=8815.6; $p<0.005$) (Table 2). Age for Public female patients varied from 12 to 97 years (M=62.68 years; SD±13.5; CI95%=61.13-64.21) and for those from the Private system, it varied from 3 to 86 years (M=44.96 years; SD±17.9; CI95%=42.72-47.20), being this difference statistically significant ($p<0.005$). Figures 2 and 3 present the number of dosages distribution in relation to Vitamin D reference serum levels (Deficiency, Insufficiency, Sufficiency), obtained after analyzing the exams done by patients, respectively, of male gender and female gender, from Public and Private system. Among the 8,046 male patients 4,989 (62%) are being attended by Public system and 3,057 (38%) belong to a Private system (Table 1). Concerning serum levels, 6,115 dosages (76%) presented Sufficiency serum levels, being 3,983 (49.5%) from Public and 2,132 (26.5%), from Private. Likewise, 1,400 (17.4%) dosages with Insufficiency were found, being 805 (10%) from Public system and 595 (7.4%) from Private. Deficiency total dosages were found in 531 (6.6%) of the cases, but being 330 (4.1%) from the Private system and 201 (2.5%) from Public. The highest prevalence found, of Sufficiency and Insufficiency serum levels in Public system and Deficiency in the Private, reveals significant difference between vitamin levels in health care systems (χ^2=168.97; $p<0.005$) (Figure 2).

Serum level values for Public male patients varied from 15.8 to 86.8 ng/mL (M=41.3 ng/mL; SD±13.89, CI95%=38.08-44.49) and for those from the Private system, varied from 17.1 to 65.9 ng/mL (M=36.1 ng/mL; SD±12.13; CI95%=32.49-39.70), being such difference statistically significant (p=0.03). In relation to Public age range, the distribution of numbers of exams by serum levels, by prevalence order, was a follows (Figure 2) - Sufficiency: 2,658 (33.05%) exams in the elderly range, 725 (9%) adult, 334 (4.15%) young adult, 133 (1.65%) infancy and 133 (1.65%) adolescence; Insufficiency: 476 (5.85%) elderly range, 265 (3.3%) adult and 64 (0.85%) young adult; Deficiency: 201 (2.5%) elderly range. In the Private system, the distribution occurred as follows - Sufficiency: 725 (9%) adult range, 607 (7.55%) young adult, 334 (4.15%) elderly, 265 (3.3%) infancy and 201 (2.5%) adolescence; Insufficiency: 398 (4.95%) adult, 133 (1.65%) young adult, 64 (0.85%) elderly; Deficiency: 133 (1.65%) adult, 133 (1.65%) elderly; 64 (0.85%) young adult. The elderly has been the most prevalent age range (~41.5%), with statistical significance (χ^2=238.93; $p<0.005$), in all Public serum levels, and adult range for the Private system (~16%), also in all serum levels and with statistical significance (χ^2=456.47; $p<0.005$), showing higher exam requests in such ranges. Infancy and adolescence were the ones with the lowest number of requests, in both health care systems (Figure 2). Among the 36,654 female patients, 19,976 (54.5%) have a Public system and 16,678 (45.5%) a Private system (Table 2).

Table 1. Distribution, in percentages, of the number of male patients from Public and Private System, according to age range

Age Range/ Health Care System	Male Public N=4,989 (62%)		Male Private N=3,057 (38%)		Total N=8,046	
	N	%	N	%	N	%
Infancy	133	1.65	265	3.3	398	4.95
Adolescence	133	1.65	201	2.5	334	4.15
Young adult	398	4.95	804	10.0	1,202	14.95
Adult	990	12.30	1,256	15.6	2,246	27.90
Elderly	3,335	41.45	531	6.6	3,866	48.05

N- number of patients

Table 2. Distribution, in percentages, of the number of female patients from Public and Private System, according to age range

Age Range/ Health Care System	Female Public N=19,976 (54.5%)		Female Private N=16,678 (45.5%)		Total N=36,654	
	N	%	N	%	N	%
Infancy	0	0.0	337	0.92	337	0.92
Adolescence	73	0.2	878	2.4	951	2.59
Young adult	1,283	3.5	6,194	16.9	7,477	20.40
Adult	9,677	26.4	7,305	19.93	16,982	46.33
Elderly	8,943	24.4	1,964	5.36	10,907	29.76

N- number of patients

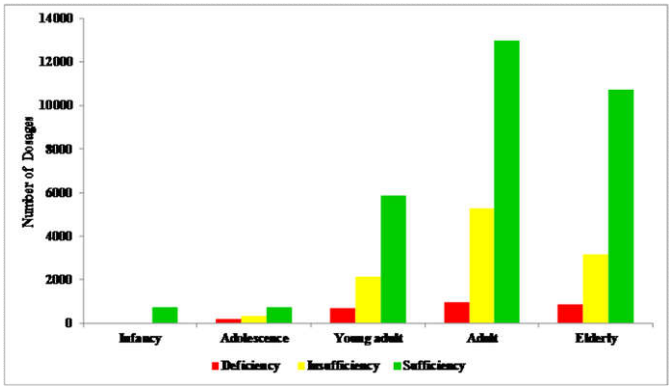

Figure 1. Distribution of the number of Vitamin D dosages, according to serum level, by patients´ age range

Concerning serum levels, 24,970 dosages (68.2%) presented Sufficiency serum levels, being 14,681 (40.06%) from Public and 10,289 (28.14%) from Private system. But, from the 9,526 (25.91%) Insufficiency dosages, 5,180 (14.06%) were from Private system and 4,396 (11.85%) from Public. Likewise, 2,158 (5.89%) Deficiency dosages were found in 1,209 (3.3%) patients from Private system and 949 (2.59%) from Public. The highest prevalence found of serum levels Insufficiency and Deficiency in the Private system and Sufficiency in Public system, revealed significant difference between vitamin levels and health care systems (χ^2=572.03; p<0.005) (Figure 3). Serum level values for Public female patients varied from 8.8 to 140 ng/mL (M=37.5 ng/mL; SD±14.5; CI95%=35.91-39.23) and for those from Private system, varied from 14.6 to 65.6 ng/mL (M=34.9 ng/mL; SD±11.5; CI95%=33.50-36.39), being this difference statistically significant (p=0.01). In relation to Public age range, the distribution of serum levels, by prevalence order, was as follows (Figure 3)- Sufficiency: 7,085 (19.5%) exams in adult range, 6,517 (17.46%) elderly, 1,006 (2.9%) young adult and 73 (0.2%) adolescence; Insufficiency: 2,089 (5.7%) elderly, 2,053 (5.6%) adult and 204 (0.55%) young adult; Deficiency: 539 (1.47%) adult, 337 (0.92%) elderly and 73 (0.2%) young adult. In the Private system the distribution of serum levels in relation to age range, by prevalence order, was as follows- Sufficiency: 4,472 (12.2%) adult range, 3,922 (10.7%) young adult, 1,221 (3.4%) elderly, 337 (0.92%) infancy and 337 (0.92%) adolescence; Insufficiency: 2,571 (7%) adult range, 1,733 (4.6%) young adult, 539 (1.47%) elderly and 337 (0.92%) adolescence; Deficiency: 539 (1.47%) young adult, 262 (0.73%) adult, 204 (0.55%) adolescence and 204 (0.55%) elderly. Adult age range was the most prevalent in both Sufficiency and Deficiency serum levels in Public System (~21%), with statistical significance (χ^2=112.53; p<0.005), as well as in the Private (~20%), but in the Private system Sufficiency and Insufficiency levels showed statistical significance (χ^2=861.56; p<0.005), configuring higher exam requirements in these ranges. As observed in the male gender, infancy and adolescence were, again, the ones with fewer requirements, in both health care systems (Figure 3).

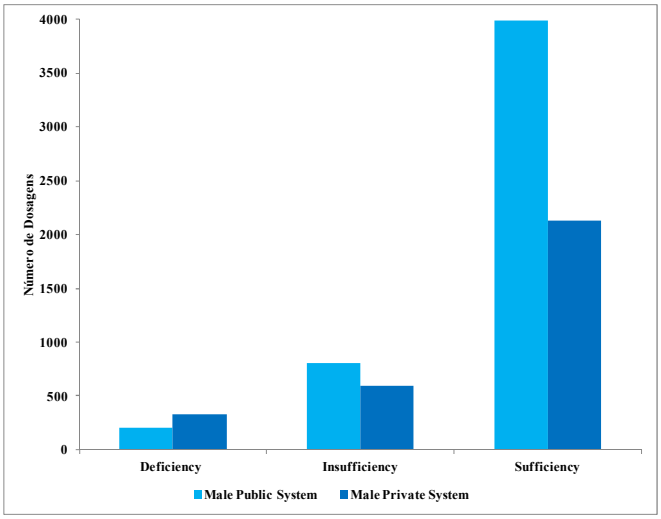

Figure 2. Distribution of the number of Vitamin D dosages, according to serum levels between male patients from Public and Private System

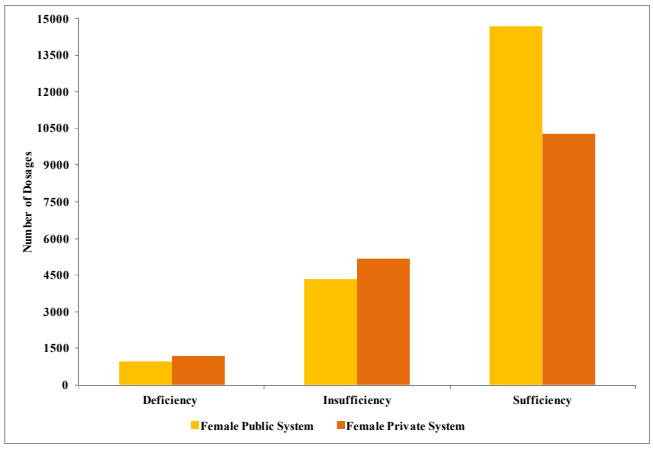

Figure 3. Distribution of the number of Vitamin D dosages, according to serum levels between female patients from Public and Private System

DISCUSSION

Although hypovitaminosis D is more frequent in undernourished patients or with chronic diseases, it has also been described in children or individuals from a more favorable socioeconomic level when Vitamin D intake or sun exposure are being insufficient (Brazilian Society of Pediatrics, 2016). The subclinical symptoms resulting from

Insufficient Vitamin D serum levels, such as bone pain and muscle weakness, can be of difficult diagnostic suspicion and going unnoticed not being, therefore, investigated (Health Quality Ontario, 2010). Considering the foregoing, based on the analysis of forty-four thousand and seven hundred laboratory test reports, the present study presents the Vitamin D serum profile of both gender patients, who did the exams in the Institution Laboratory by the Private or by the Public health care system, in routine consultation, in a five-year period (2012-2016). Regarding the data related to gender and health care systems, among the analyzed reports, the highest prevalence obtained, of lab exams requests to assess Vitamin D serum levels, was for female gender (82%), being in agreement with the literature (Gobbi *et al.*, 2016), and carried out by Public (~56%). Gender prevalence may be explained because, besides women being from a risk group, they are more worried about going to preventive routine consultation than men, as about 40% of men do not seek for attendance in basic care (Oliveira *et al.*, 2015).

As to serum levels and health care systems in male gender, the highest prevalence found of Sufficiency and Insufficiency was in the Public system, and of Deficiency in the Private. In the female gender, the highest prevalence found of Insufficiency and Deficiency was in the Private system and of Sufficiency in the Public. There are no data in the literature to compare gender and serum levels with health care systems. Epidemiological and meta-analysis studies reveal that Vitamin D Deficiency has high global prevalence, not only in the risk group which includes children, pregnant women, the elderly, the institutionalized, chronic patients (van Schoor *et al.*, 2011), but also in individuals out of such a group, in infancy and adolescence range, in European and North-American countries (Huh *et al.*, 2006). In the Middle East and Asia, Deficiency serum levels are highly prevalent in adult range (van Schoor *et al.*, 2011; Edwards *et al.*, 2014). Nevertheless, real global prevalence of insufficient or deficient Vitamin D serum levels remains uncertain, since there is a lack of data from many countries or data which are outdated (Palacios *et al.*, 2014), especially in South America, where most studies presented non-representative case study results and with the inclusion of risk groups (van Schoor *et al.*, 2011). In the present study, individuals from all age ranges (infancy to the elderly) in routine outpatient consultations were included, excluding pregnant women, hospitalized, transplanted, institutionalized people, people with chronic diseases or people making use of vitamin supplementation, what has not occurred in most studies of the literature (van Schoor *et al.*, 2011; Edwards *et al.*, 2014; Palacios *et al.*, 2014). In the case study of this study (44,700) the prevalence of Sufficiency has been found in 69.5% of cases, Insufficiency in 24.5% and Deficiency in 6% of cases, after the analysis of exams carried out in a five-year period, in a single laboratory.

A meta-analysis study in European countries, with case study of 55,844 individuals of all age ranges, including the risk ones, revealed the prevalence of altered Vitamin D serum levels in 40.4% of cases - Deficiency and Insufficiency added, due to the differences in the methodologies of laboratory dosages between the various studies analyzed (Cashman *et al.*, 2016). In the present study, the prevalence was 30.5%, both levels added, with the same laboratory technique in all exams performed. This prevalence determined is of extreme relevance, when compared to the total found in Europe. Due to the scarce number of publications, ethnic, regional and geographic diversity, a literature revision was carried out in order to identify articles with results which indicated the global prevalence of Vitamin D, over the last ten years, in apparently healthy individuals, also including the risk group ones (Palacios *et al.*, 2014). In this revision, it has been affirmed the existence of few data regarding age ranges of infancy and adolescence in most countries of South America and Africa (van Schoor *et al.*, 2011; Palacios *et al.*, 2014). But, the results also came from studies which used different laboratory methods for Vitamin D serum dosage. Anyway, the results specifically related to Brazil were: lack of data published about Vitamin D Deficiency in infancy and adolescence, 77% of Deficiency in adults and 62% in the elderly. In women, the prevalence was 36% of Deficiency and 91% of Insufficiency. Regarding pregnant women or infants there has not been published data either (Palacios *et al.*, 2014). In the present study, after report analyses from a single laboratory, concerning age range, it has been found a total prevalence of 24.5% of Insufficiency and 6% of Deficiency of Vitamin D in all age ranges, except for infancy, being these differences statistically significant. In infancy range, due to the few dosage requests, which revealed Sufficiency in only 1.6%, it is difficult to tell whether or not there are cases of Deficiency or Insufficiency in this age range. Despite the fact that a few dosages have been carried out, the data obtained in infancy were different from the literature ones (Palacios *et al.*, 2014).

Still concerning age range, a Brazilian study evaluated Vitamin D serum levels in 3,409 patients over the age of 40, being the data also collected from the data bank of one laboratory in town, for a ten-month period (Gobbi *et al.*, 2016). Differently from the present study, higher prevalence has been found for Insufficiency and Deficiency levels, but this case study was composed only by adult and elderly patients, making use of vitamin complementation. Publications resulting from meta-analysis of Vitamin D serum levels space distribution are still scarce, especially in tropical countries. Extensive review study investigated the prevalence and space distribution of Vitamin D Deficiency and Insufficiency in the Brazilian population, during seventeen years (2000-2017) and, the total prevalence found was: Deficiency - 28.6% and Insufficiency - 45.27%. In relation to regional distribution, the highest Deficiency prevalence was observed in the Southeast (31.11%) and South (30.28%) regions and Insufficiency was Southeast (54.57%) and Northeast (51.36%) regions (Pereira Santos *et al.*, 2018). In the present study the Deficiency (6%) prevalence found represents about 1/5 of the results of entire Southeast region (Pereira Santos *et al.*, 2018) and Insufficiency (24.5%) represents the approximate prevalence of the whole Northern region (26.5%) (Pereira Santos *et al.*, 2018). In low latitude locations, about 90% of the amount of Vitamin D is derived from cutaneous synthesis after sun exposure, occurring in most part of the year (Tsiaras *et al.* 2011). However, paradoxically, studies on populations from tropical countries report prevalence of Vitamin D Deficiency and Insufficiency (Pereira Santos *et al.*, 2018; Unger *et al.*, 2010; Santos *et al.*, 2012), as found in the present work, possibly for not occurring adequate supplementation or intake of Vitamin D (Huh *et al.*, 2006). Similar results have been observed in another meta-analysis study which describes the occurrence of Vitamin D Deficiency and Insufficiency in different populations around the globe, including countries with reduced solar incidence (Hilger *et al.*, 2014). Evidence in the literature suggests that Vitamin D Deficiency may be considered a public health

problem, for affecting the population in all age ranges. The quantification of Vitamin D in foods and the elaboration of tables, with nutritional values, must be part of the planning of an adequate policy of supplementary fortification (Hoteit *et al.*, 2014; Jääskeläinen *et al.*, 2017).

Conclusion

The analysis of the Vitamin D serum profile of patients, in routine consultation, allows the conclusion that there has been a higher prevalence of exams requests for female gender and by the Public system. However, Deficiency and Insufficiency levels have been found in both genders in all age ranges except for infancy, in the Private system and female gender prevailing in both serum levels. The prevalence of Vitamin D serum levels of Deficiency and Insufficiency in individuals, in routine consultations, allows drawing attention to reassess the need to request dosages, in this group, as a preventive measure in order to avoid the consequences arising from inadequate Vitamin D concentrations.

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