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Hypovitaminosis D in a sunny country: Time trends, predictors, and implications for practice guidelines

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ABSTRACT

The aim of the current study is to investigate the prevalence of hypovitaminosis D in Lebanese subjects, its robust predictors, evaluate the relationship between 25 hydroxy vitamin D [25(OH)D] and parathyroid hormone levels, and derive desirable vitamin D levels, based on a large hospital laboratory database spanning all age groups.

Data from a large representative digitized database of 9147 subjects, mostly outpatients, evaluated between 2000–2004 and 2007–2008, in whom information on age, gender, service, and time of the year, was analyzed. The PTH–25(OH)D relationship was studied in a subset of 657 adult subjects, in whom such data were available.

At a 25(OH)D cut-off of < 20 ng/ml, the prevalence of hypovitaminosis D ranged between 58% and 62% in pediatric subjects, 44% and 60% in adults, and 41% and 62% in elderly, in the 2 study periods. At a cut-off <30 ng/ml, the prevalence was above 78%, in most sub-groups. Regardless of cut-off used, the only significant predictors of high mean 25(OH)D levels were the male gender in the pediatric group, and female gender in adults and elderly, summer/fall seasons, out-patient status, as well as study period. Curve fitting of the PTH–25(OH)D relationship, in adults and elderly, revealed a plateau at 25(OH)D levels of 17–21 ng/ml, depending on sub-study group.

Hypovitaminosis D is prevalent in our sunny country, even using a conservative population-derived cut-off of 20 ng/ml, and thus the need for a public health strategy for supplementation.

Abbreviations: (PTH)-25(OH)D, Parathyroid hormone-25 hydroxy-vitamin D; ES, Endocrine Society; IOM, Institute of Medicine; AUB-MC, American University of Beirut-Medical Center; SCa, Serum calcium; SP04, Phosphorus; ALKP, Alkaline phosphatase; PTH, Parathyroid hormone; SCr, Serum creatinine; IDS, Immuno Diagnostic Systems; DEQAS, Vitamin D External Quality Assurance Surveillance; SD, Standard deviation; OR, Odds ratio; ANOVA, Analysis Of Variance; NHANES III, National Health And Nutrition Survey III.

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1. Introduction

Vitamin D is a steroid hormone with beneficial effects on musculoskeletal health throughout the lifecycle [1,2]. An increasing body of evidence also supports additional pleotropic effects [3]. Serum 25(OH)D level is the best index of vitamin D nutritional status. Prevalence of 25(OH)D insufficiency ranges between 50% and 90%, depending on the cut-off used, and population of interest [1,2]. Countries with the highest prevalence are in Asia in general and the Middle East in particular [1,4–7]. Studies on the prevalence of hypovitaminosis D in this region have in large part been conducted on small, non-population based studies, and failed to cover all age groups, risk factors, and time trends within the same study/country [8]. Furthermore, many have used different assays to measure 25(OH)D, a major limitation in comparing results across age groups and genders, in view of the wide assay variations reported [9–11].

The desirable 25(OH)D levels, and thus hypovitaminosis D, have been a matter of great debate lately, set at 30 ng/mL (75 nmol/L) in the 2011 Endocrine Society (ES) 25(OH)D guidelines [12], but only at 20 ng/mL (50 nmol/L) in the 2010 Institute of Medicine report (IOM) [13]. However such cut-offs were defined almost exclusively based on data from western countries, and for the most part from older populations [14].

The objectives of this study were to investigate the prevalence of hypovitamonosis D in Lebanon, a sunny country, using international guideline based cut-offs, and determine major risk factors for low vitamin D levels, both in inpatients and in outpatients. This was achieved using data derived from a large laboratory-based database, gathered across a wide temporal window, and that included all age groups, and both genders.

2. Materials and Methods

2.1. Study Population and Laboratory Methods

This was a retrospective study in Lebanese inpatients and outpatients, receiving care at the American University of Beirut-Medical Center (AUB-MC), from the period 2000 to 2004 and from 2007 to 2008. Beirut is located 33° North, enjoys a temperate climate and over 300 days of sunshine per year, as per the official website of the Beirut airport [http://www.beirutairport.gov.lb/_TouristInfo.php accessed on May 2013].

AUB-MC is a University based academic center in Lebanon that attracts patients from all regions of the country, and from differing socioeconomic levels. Anonymized demographic and laboratory data on patients who had 25(OH)D level measured in the period from 2000 to 2004 and from 2007 to 2008 were retrieved using the central digitized laboratory database of the Clinical Pathology Laboratory. For patients who also had a serum calcium (SCa), phosphorus (SP04), alkaline phosphatase (ALKP), parathyroid hormone (PTH), and serum creatinine (SCr) levels measured, such information was also retrieved. Subjects with hypocalcemia, hypercalcemia, and/or high PTH levels, with the exception of those with secondary hyperparathyroidism from non-renal causes, were excluded. Patients with possible mild hyperparathyroidism, defined by the presence of a SCa level at mid-upper limit of normal, normal SCr and high PTH levels were also excluded. The above was determined by examining individual values against normative laboratory ranges, defined in Appendix I. Laboratory data were available for a total of 9147 subjects, in both study periods. Subgroup analyses were performed by age strata (the pediatric population was defined as subjects ≤18 years, adults those with ages 19–64 years, and elderly age ≥65 years), gender and time period, and SCr levels above upper limit. Because of the significant impact of renal failure on indices of mineral metabolism, subgroup analysis including patients with a SCr > 1.0 mg/dl in female subjects and SCr > 1.2 mg/dl in male subjects, was also implemented and included in appendices. The study was approved by the Institutional Review Board at AUB-MC.

Routine chemistries were measured in the Clinical Chemistry laboratory at AUB-MC, using the auto-analyzer Hitachi 912 (Roche Diagnostics GmBH, Mannheim, Germany) before 2007, and the auto analyzer Roche Modular Analytics afterwards (Roche Diagnostics GmBH, Mannheim, Germany) after 2007. SCr level was measured using Jaffé reaction assay before 2007 and Kinetic colorimetric assay after 2007. Serum 25(OH)D and PTH levels were measured in the Endocrine Core laboratory. For the most part, and in both study periods, serum 25(OH)D was measured with the IDS (Immuno Diagnostic Systems) liquid-phase radio-immunoassay kit (Immunodiagnostic systems (IDS) 10 Didcot Way, Boldon Business Park, Boldon, USA). This was with the exception from 2000 to 2002 when both the IDS and the Incstar Diasorin kits were used interchangeably, testing both kits before a switch was made to the IDS assay. Mean 25(OH)D levels before and after the switch did not differ (data not shown). Diasorin is a competitive protein binding (Diasorin, Incstar, Saluggia, Italy), with intra and inter-assays CVS of less than 13% at a serum concentration of 47 ng/ml. For the IDS assay, the cross-reactivity is reported by the manufacturer to be 75% to 25 $(OH)D_2$ and 100% to 25$(OH)D_3$ (www.idsplc.com). The reportable range of the assay is 3.36–210 pg/ml. The manufacturer reports an intra-assay precision (CV) is 5.0%–6.1% for values between 10.6 and 60.4 ng/ml and the inter-assay precision (CV) of 7.3%–8.2%, for values between 7.84 and 54.4 ng/ml. In our laboratory, the intra-assay precision (CV) (assayed in duplicates) is 4.62% ± 2.9%, and the inter-assay precision is 5.9% ± 5.9%, based on a sample of 10 patients. Serum intact PTH level were measured with ELSA-PTH immunoradiometric assay (Cis Bio International, Gif-Sur-Yvette, Cedex, France). The manufacturer's normal range for PTH is 8–76 pg/mL, the detection limit of the assay is 0.7 pg/mL, and the intra-assay and inter-assay coefficients of variation are below 7% at PTH concentrations 6 to 95 pg/mL. Hormonal assays were run in duplicates and the mean value reported. The normative ranges for all laboratory tests in our laboratory are summarized in Appendix I.

The Endocrine Core Laboratory is a participant in the Vitamin D External Quality Assurance Surveillance (DEQAS, program, www.deqas.org) since 2002, and the Clinical Chemistry laboratory partakes in the quality assurance, evaluation, and accreditation from the College of American Pathologists (www.cap.org).

2.2. Statistical Analyses

Continuous data were summarized using means and standard deviation (SD) or medians with ranges as applicable, whereas categorical variables were presented as percentages and counts. Numbers were rounded to the first decimal, except for the odds ratio (OR), rounded to second decimal. Differences in the 25(OH)D levels between groups were tested using either independent t-test or Mann–Whitey Test as appropriate, Analysis of Variance (ANOVA) or its nonparametric equivalence, the Kruskal–Wallis test. Categorical variables were also compared using Chi-square test. Multivariate logistic regression was performed for exploring possible predictors of low 25 (OH)D levels, at different cutoff points, 20 ng/ml and 30 ng/ml. ORs for proportions below these cutoffs and their confidence intervals are reported. Different non-linear regression models were used to describe the PTH–25(OH)D relationship and define a population specific desirable vitamin D level. The best fit was selected based on the iterative non-linear least squares fitting method that shows the highest value in the coefficient of determination (R^2). The equation defining the exponential decay relationship is:

$$iPTH = a + b\ \exp[c \times 25(OH)D]$$

where iPTH plateau is usually reached when 25(OH)D = 3/c. Considering that PTH–25(OH) D relationship cannot have a zero value for 25(OH) D level, the equation was modified as follows:

$$iPTH = a + b \exp[c \times (25(OH)D - \min 25(OH)D]$$

where min 25(OH)D is the minimum value of 25(OH)D in our sample. In order to detect the plateau value for 25(OH)D, rolling decile groups of increasing lowest 25(OH)D levels were used to characterize the relationship between PTH and 25(OH)D. In this method, the 657 adults and elderly who had dual measurements of both PTH and 25(OH)D levels were first arranged in increasing 25(OH)D level order, and a total of 19 subgroups (50% overlap) were separately analyzed, such that group 1 included patients from 1 to 66 (0%–10%), group 2 included patients from 33 to 99 (5%–15%), and so on, as described before [15]. Using this method, the small subgroup size would minimize the with-in group heterogeneity, and the 50% overlapping ranges of the independent variable (25(OH)D), as compared to the 75% overlapping ranges, provided a better fit by ensuring a more gradual description of the relationship between the two variables [16]. Similar analysis was implemented after stratifying by gender, and after including those with high SCr levels

Table 1 – Demographic and clinical characteristics of the study population in periods from 2000 to 2004 and periods from 2007 to 2008.

		2000–2004		2007–2008		
		N = 3751 N	(%)	N = 5135 N		(%)
Pediatric (0–18 years)		**N = 231**		**N = 349**		
Age (years) *		10 ± 5.8		12.2 ± 4.5		
Gender	Female	128	(55%)	202		(58%)
	Male	103	(45%)	147		(42%)
Hospital services	Inpatient	28	(12%)	57	†	(16%)
	Outpatient	203	(88%)	291		(84%)
Season	Jan–March	49	(21%)	76		(22%)
	Apr–June	55	(24%)	95	†	(27%)
	July–Sept	62	(27%)	91		(26%)
	Oct–Dec	65	(28%)	86		(25%)
Adult (19–64 years)		**N = 2386**		**N = 3024**		
Age (years) *		49.2 ± 11.4		49.5 ± 11.6		
Gender	Female	2052	(86%)	2552		(84%)
	Male	334	(14%)	472		(16%)
Hospital services	Inpatient	223	(9%)	94	†	(3%)
	Outpatient	2163	(91%)	2928		(97%)
Season	Jan–March	558	(23%)	643		(21%)
	Apr–June	665	(28%)	764	†	(25%)
	July–Sept	679	(29%)	754		(25%)
	Oct–Dec	484	(20%)	855		(29%)
Elderly (≥65 years)		**N = 1134**		**N = 1762**		
Age (years) *		71.8 ± 5.4		72.7 ± 5.7		
Gender	Female	906	(80%)	1444		(82%)
	Male	228	(20%)	318		(18%)
Hospital services	Inpatient	210	(18%)	115	†	(6%)
	Outpatient	924	(82%)	1646		(94%)
Season	Jan–March	266	(24%)	450		(26%)
	Apr–June	299	(25%)	426	†	(24%)
	July–Sept	301	(27%)	395		(22%)
	Oct–Dec	268	(24%)	2489		(28%)

* Mean ± SD.

† Numbers do not add up to total N in that age group due to missing data (N = 1–8, 0.1%–0.3% for the variables of interest).

identified according to the set cutoff points. P value ≤ 0.05 was used to indicate significance of tests. Analyses were performed using SPSS version 20.0 (IBM, USA) and SigmaPlot 12.0 (Systat Software Inc., San Jose, CA).

3. Results

3.1. Demographic Characteristics

From 2000 to 2004, data were available on a total of 3751 subjects: 231 pediatric subjects (10 ± 5.8 years; 55% females), 2386 adults (49.2 ± 11.4 years; 86% females) and 1134 elderly (71.8 ± 5.4 years; 80% females). In the period from 2007 to 2008, the total number of subjects was 5135, 349 pediatric subjects (12.2 ± 4.5 years; 58% females), 3024 adults (49.5 ± 11.6 years; 84% females) and 1762 elderly (72.7 ± 5.7 years; 82% females). These numbers and proportions, in both time periods, were unchanged after including 261 subjects with SCr levels above upper limit of normal, mean SCr = 1.7 ± 1.2 mg/dl in adults and elderly, and median SCr = 0.6 [0.5–0.7] mg/dl in children with median age of 7 [4–8] years. Subjects' characteristics are presented in Table 1 for subjects with normal SCr and in Appendix II in the overall sample including those with mild elevation in SCr.

3.2. Mean Serum 25(OH)D Level

There was a consistent trend for a rise in mean serum 25(OH)D level between the period from 2000 to 2004, and from 2007 to 2008, across all age sub-groups and genders in those with normal SCr (Figs. 1 and 2) and including those with high SCr levels (Figure Appendices III and IV). Analyses for the two study periods were thus conducted separately. In general, median 25(OH)D level was below 20 ng/ml in pediatric subgroups at both time periods, and similarly was the mean in the adults–elderly subgroup, but only from 2000 to 2004 (Table 2).

Study period from 2000 to 2004: In the pediatric age group, median level of 25(OH)D was significantly higher in younger subjects (age < 10 years), in males, and there was a trend for it to be high in outpatients. It was lowest in the winter season (January–March). While there was no clear gender difference in adults, levels were significantly higher in elderly women than men. Conversely, a seasonal effect could be demonstrated in adults but not the elderly, the highest levels were in summer and fall. Outpatients had consistently higher levels than inpatients, both in adults and in elderly (Table 2). These numbers and proportions did not differ when including subjects with high SCr (Appendix V).

Study period from 2007 to 2008: In the pediatric age group, median level of 25(OH)D was significantly high in younger subjects (age < 10 years), in males, was lowest in the winter season (January-March), and tended to be higher in outpatients (Table 2). In general, both in adults and in elderly, mean 25(OH)D level was higher in female subjects, in the outpatient setting, and during the summer and fall (Table 2). These numbers and proportions did not differ when including subjects with high SCr (Appendix V).

Additional analyses for mean 25(OH)D level by age sub-groups, 20–49, 50–64, > 65 years, revealed no differences in male subjects, for the period 2000 to 2004, and 2007 to 2008. Conversely, women in the 50–64 years age sub-group had the highest mean 25(OH)D level compared to the other 2 subgroups, with mean values that were on the average 1–4 ng/ml higher than in the other two subgroups, p < 0.001. Similar findings were obtained upon including those with high SCr levels (data not shown).

Serum 25(OH)D level, by gender, patient hospital status and season, is shown for the pediatric (Fig. 1) and the adult–elderly age groups (Fig. 2) in subjects with SCr; and in the overall group (Appendix III and Appendix IV).

In the pediatric group, there was a small rise in median 25 (OH)D level of 2–5 ng/ml between the two time periods. Median 25(OH)D level was 2–5 ng/ml higher in boys than girls, and 6–8 ng/ml higher in the summer compared with the winter season (Fig. 1). In adults, there was a small rise in mean 25(OH)D level of 2–5 ng/ml between the two time periods.

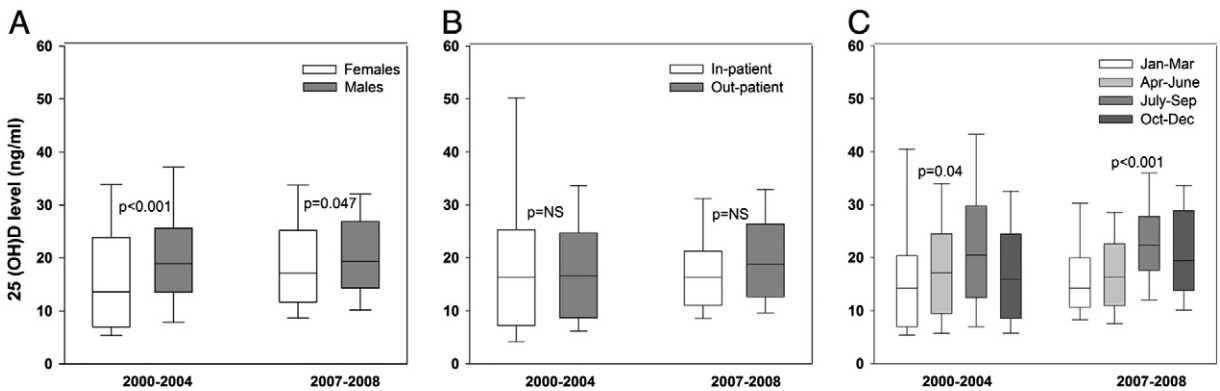

Fig. 1 – Box plot for median levels of 25(OH)D with 25th–75th percentiles in pediatric subjects, in two time periods, by gender, hospital services, and season. There was a small increase in median levels of 25(OH)D, in 2007–2008 compared to 2000–2004, in females (p = 0.001), outpatients (p = 0.008), and in the fall (p = 0.014). Within the same time period, males had higher level of 25 (OH)D than females, 25(OH)D was significantly different within seasons, but there was no difference in 25(OH) D between inpatients and outpatients.

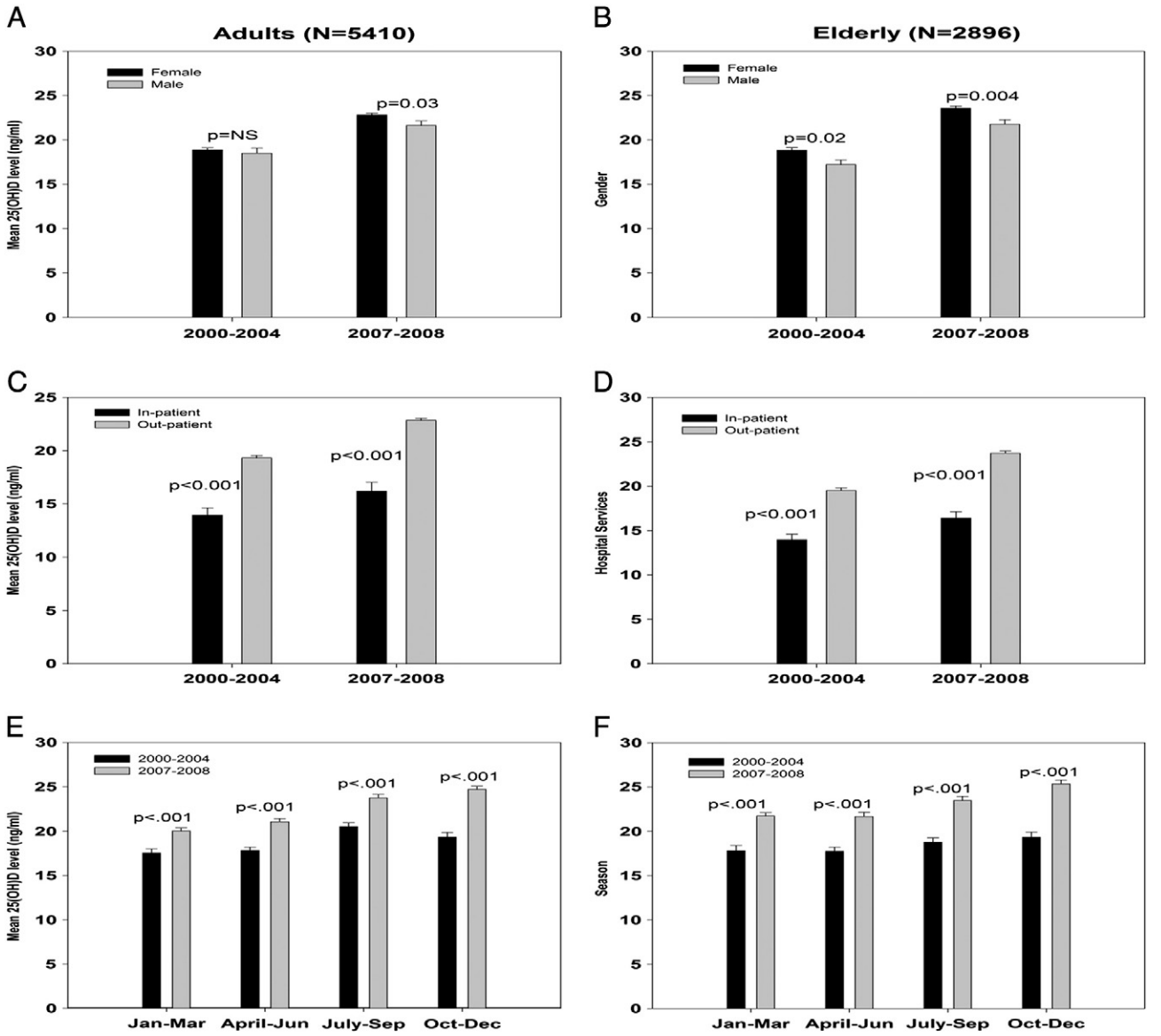

Fig. 2 – Mean levels of 25(OH)D in adults (left panels) and elderly subjects (right panels) in two time periods, by gender, hospital services, and season. There was a significant increase in mean levels of 25(OH)D in 2007–2008 compared to 2000–2004 in both genders ($p < 0.001$), in all seasons ($p < 0.001$), in outpatients ($p < 0.001$) of both age groups, except for adult inpatients. For the same time period, females had higher levels of 25(OH)D than males except for adults in 2000–2004, outpatients had higher levels of 25(OH)D compared to inpatients, summer and fall seasons had the highest levels of 25(OH)D.

Mean serum 25(OH)D levels were 1.5–2 ng/ml higher in females, 5–6 ng/ml higher in summer–fall compared to winter, and 6–7 ng/ml higher in outpatients compared to inpatients (Table 2 and Fig. 2).

3.3. *Prevalence of Hypovitaminosis D*

3.3.1. *IOM cut-off of 20 ng/ml*

The proportion of subjects below this cut-off, considering all possible subgroups, gender, season, age, patient hospital status, study period, was over 40% (Appendix VI-A). The prevalence of hypovitaminosis D was 63% in pediatric subjects, 60% in adults, and 62% in elderly in the period from 2000 to 2004; the proportions were 58 % of pediatric subjects, 44% of adults and 40% of elderly, in the period from 2007 to 2008 (Appendix VI-A). The lower proportions in the second study period reflect the observed systematic rise in mean 25(OH)D level between the two study periods, as described above.

3.3.2. *ES cut-off of 30 ng/ml*

The proportion of subjects below this cut-off, considering all possible subgroups (gender, season, age, patient status, years) was over 78% (Appendix VI-B). The prevalence of hypovitaminosis D was 84% in pediatric subjects, 88% in adults, and 90% in elderly, in the periods from 2000 to 2004; and the proportions were 87% in pediatric subjects, 78% in adults, and 79% in elderly, in the period from 2007 to 2008.

Table 2 – 25(OH)D levels in the period of 2000 to 2004 and 2007 to 2008, by age, gender, season and hospital services.

		2000–2004			2007–2008		
		N	25(OH)D† (ng/ml)	P value*‡	N	25(OH)D† (ng/ml)	P value*‡
Pediatric (0–18 years)			**N = 231**			**N = 349**	
Gender	Female	128	13.5[1.3–79.2]	**<0.001**	202	17.1[5.4–67]	**0.047**
	Male	103	18.9[1.9–67]		147	19.3[5.9–74.2]	
Hospital services	Inpatient	28	16.3[1.3–55.7]	**0.57**	57	16.3[6.8–42.3]	**0.067**
	Outpatient	203	16.6[1.8–79.2]		291	18.8[5.4–74.2]	
Season	Jan–March	49	14.2[1.3–67]	**0.04**	76	14.2[5.4–67]	**<0.001**
	Apr–June	55	17.1[1.8–59.5]		95	16.3[5.6–48.4]	
	July–Sept	62	20.5[4.1–79.2]		91	22.4[6.8–74.2]	
	Oct–Dec	65	15.9[1.9–49.9]		86	19.5[7–45.6]	
Age category	<10 years	89	19.5[1.8–59.5]	**0.01**	88	21.5[5.6–48.4]	**0.008**
	10–15years	75	15.5[2.9–49.3]		122	17.9[5.9–74.2]	
	15–18years	67	13.7[1.3–79.2]		139	16.7[5.4–54.2]	
Adult (19–64 years)			**N = 2386**			**N = 3024**	
Gender	Female	2052	18.9 ± 10.7	**0.55**	2552	22.8 ± 10.3	**0.03**
	Male	334	18.5 ± 10.6		472	21.6 ± 10.8	
Hospital services	Inpatient	233	13.9 ± 10.4	**<0.001**	94	16.2 ± 8.2	**<0.001**
	Outpatient	2163	19.3 ± 10.6		2928	22.8 ± 10.4	
Season	Jan–March	558	17.5 ± 11.4	**<0.001**	643	20.1 ± 9.2	**<0.001**
	Apr–June	665	17.8 ± 9.2		764	21.2 ± 10	
	July–Sept	679	20 ± 11		754	23.8 ± 11	
	Oct–Dec	484	19.4 ± 10.9		855	24.8 ± 10.4	
Elderly (≥65 years)			**N = 1134**			**N = 1762**	
Gender	Female	906	18.8 ± 9.3	**0.02**	1444	23.6 ± 10	**0.004**
	Male	228	17.2 ± 8.1		318	21.8 ± 9	
Hospital services	Inpatient	210	14 ± 8.8	**<0.001**	115	16.4 ± 7.8	**<0.001**
	Outpatient	924	19.5 ± 8.9		1646	23.7 ± 9.9	
Season	Jan–March	266	17.8 ± 10	**0.09**	450	21.9 ± 8.2	**<0.001**
	Apr–June	299	17.8 ± 8.3		426	21.9 ± 10.6	
	July–Sept	301	19 ± 8.6		395	23.6 ± 9.9	
	Oct–Dec	268	19.4 ± 9.4		489	25.4 ± 10.3	

* T-test is used to compare 25(OH)D levels between genders, and between inpatients and outpatients in adults and elderly and Mann–Whitney test in pediatric patients.
† Mean ± SD or Median [min–max].
‡ ANOVA is used to compare 25(OH)D levels between seasons in adults and elderly, and Kruskal–Wallis between age categories in pediatric patients.

Including subjects with elevated SCr did not affect these findings in all age groups studies and in both study periods (Appendices VII-A and VII-B).

3.4. *Predictors of Hypovitaminosis D*

3.4.1. *IOM cut-off of 20 ng/ml*

Table 3 shows the ORs for having a 25(OH)D below this cut-off, after adjustments for all other significant predictors described above, namely age group, gender, season, hospital status and study period.

In the pediatric age group, study period, season, age, and type of hospital services were significant predictors for a 25(OH)D < 20 ng/ml. Indeed, the likelihood of having a mean 25(OH)D level below 20 ng/ml was lowered by 41% in the second study period, by 80% in the summer (July–September vs January–March), by 46% in outpatients compared with inpatients, and was increased by 12% for every one year increase of age.

In older subjects, age, gender, study period, season, type of hospital services, were predictors for 25(OH)D < 20 ng/ml. Indeed, the likelihood of having a mean 25(OH)D level below 20 ng/ml was lowered by 47% in the second study period, by 38% in the summer (July–Sept vs January–March), by 68% in outpatients compared with in patients, and by 13% in elderly compared to adults. Males had a 21% higher risk of being below this desirable vitamin D level compared to females. There was a significant season by year interaction, in adults, with patients in the fall season, (p = 0.009) as detailed in Table 3.

3.4.2. *ES cut-off of 30 ng/ml*

Using this higher cut-off, the impact of age, seasonal variation, and gender was less pronounced (in terms of magnitude of OR estimates) and less consistent, in the adjusted analyses, both in children and in adults (see Table 3). Study period, gender, season and type of hospital services were significant predictors for 25(OH)D below 30 ng/ml in adults, while only age and season were in the pediatric age group (Table 3).

3.5. *Seasonal Variation of 25(OH)D Levels In All Age Groups*

Mean levels of 25(OH)D for each month were derived in children (N between 36 and 81 per month), adults (N between 350 and 543 per month), and elderly subjects (N between 207 and 272 per month), with normal SCr levels. There are

Table 3 – Likelihood of having mean level of 25 (OH)D below specific cutoffs < 20 ng/ml and < 30 ng/ml by age category.

Predictors of low 25(OH) D	25(OH)D <20 ng/ml		25(OH)D <30 ng/ml	
	OR* [95% CI]	P value	OR* [95%CI]	P value
Pediatric Group				
Years (2007–2008 vs 2000–2004)	0.59[0.41–0.87]	**0.007**	0.90[0.55–1.48]	**0.68**
Age	1.12[1.08–1.16]	**<0.001**	1.11[1.06–1.16]	**<0.001**
Male (vs female)	0.71[0.50–1.02]	**0.11**	0.86[0.53–1.39]	**0.54**
Season (vs Jan–March)		**<0.001**		**0.003**
Apr–June	0.66[0.38–1.14]	**0.14**	1.28[0.57–2.92]	**0.55**
July–Sept	0.20[0.11–0.34]	**<0.001**	0.38[0.19–0.78]	**0.01**
Oct–Dec	0.40[0.23–0.69]	**0.001**	0.51[0.24–1.05]	**0.07**
Hospital services (outpatient vs inpatient)	0.54[0.32–0.93]	**0.03**	0.91[0.46–1.80]	**0.80**
Adults and Elderly Group				
Years (2007–2008 vs 2000–2004)	0.53[0.44–0.64]	**<0.001**	0.62[0.46–0.84]	**0.002**
Elderly (vs adults)	0.87[0.79–0.95]	**0.003**	1.06[0.94–1.21]	**0.33**
Male (vs female)	1.21[1.08–1.36]	**0.003**	1.43[1.20–1.70]	**<0.001**
Season (vs Jan–March)		**<0.001**		**0.002**
Apr–June	0.87[0.71–1.06]	**0.16**	1.02[0.73–1.41]	**0.93**
July–Sept	0.62[0.51–0.75]	**<0.001**	0.60[0.45–0.82]	**0.001**
Oct–Dec	0.72[0.58–0.88]	**0.002**	0.68[0.49–0.94]	**0.02**
Hospital services (outpatient vs inpatient)	0.32[0.26–0.38]	**<0.001**	0.31[0.22–0.44]	**<0.001**
Season † Years		**<0.001**		**0.012**
Apr–June	1.20[0.93–1.55]	**0.16**	0.77[0.52–1.15]	**0.21**
July–Sept	1.12[0.87–1.45]	**0.38**	0.93[0.64–1.34]	**0.68**
Oct–Dec	0.69[0.54–0.91]	**0.009**	0.57[0.39–0.84]	**0.004**

* The ORs presented in this Table are adjusted for all other predictors detailed in the Table.
† Represents the interaction between the two variables.

statistically significant monthly variations within each age group, reflected in the lowest levels of 25(OH)D in February and highest levels in August in the pediatric age group (Fig. 4).

3.6. 25(OH)D–PTH Relationship

The relationship between 25(OH)D and PTH was defined from data obtained on 657 adults and elderly (age 59 ± 14 years; 79% females), in whom such data were available. The mean level of SCa was 9.5 ± 0.5 mg/dl, SP04 was 3.7 ± 0.6 mg/dl, PTH was 43.2 ± 31.7 pg/ml, and 25(OH)D was 23.1 ± 10.7 ng/ml. The same analyses and curve fitting were implemented on 699 adults and elderly, including those with elevated SCr levels (age 60 ± 14 years; 78% females). The mean level of SCa for that group was 9.5 ± 0.6 mg/dl, SP04 was 3.7 ± 0.7 mg/dl; PTH was 44.3 ± 34.9 pg/ml, and 25(OH)D was 23.0 ± 10.7 ng/ml.

The non-linear regression best curve fit for the PTH–25(OH) D relation was defined by the following equation: iPTH = 38.81 + 31.42 exp[−0.34(25(OH)D − 7.99]; R^2 = 0.94, plateau 16.8 ng/ml (Fig. 3A). Including the 42 subjects with high SCr, the equation derived was iPTH = 38.95 + 34.98 exp[−0.29(25 (OH)D − 7.84]; R^2 = 0.96, plateau was reached at 18.1 ng/ml (Figure Appendix VIII-A). Plotting mean values for PTH levels by pre-set discrete decremental sub-groups of mean 25 (OH)D level, only shows a substantial rise in PTH at 25 (OH)D levels below 10 ng/ml (Fig. 3B and Figure Appendix VIII-B).

3.6.1. Gender specific analyses

The relationship between 25(OH)D and PTH was also studied in the subgroup of 519 women, (59.2 ± 14.0 years), and in 138 men (59.9 ± 15.0 years), with normal biochemical and hormonal levels for PTH and 25(OH)D. The equation in females was:

iPTH = 39.5 + 36.8exp[−0.357(25(OH)D − 7.74]; R^2 = 0.89, and the plateau was reached at a mean 25(OH) D of 16.1 ng/ml. In male subjects, the model fit was suboptimal due to the small sample size (data not shown). When including those with high SCr, the equation of females (n = 543) was: 39.29 + 29.46exp[−0.22(25(OH)D − 7.69]; R^2 = 0.91, and the plateau was reached at a mean 25(OH)D of 21.1 ng/ml and in male subjects (n = 156) the equation was iPTH = 36.44 + 36.88 exp[−0.29(25(OH)D − 8.63]; R^2 = 0.88, with a plateau at a mean 25(OH) D of 18.3 ng/ml (data not shown).

4. Discussion

The present study shows that over 40% of subjects had a 25(OH)D level below 20 ng/ml, and over 78% had levels below 30 ng/ml; with greater proportions in high risk sub-groups. Being a boy in children and adolescents, and a female in adults and elderly, an outpatient, having measurement taken in the summer and or fall, and in the period from 2007 to 2008 were independent predictors of higher mean 25(OH)D level. PTH levels seem to plateau at 25(OH) levels between 17 and 21 ng/ml, closely approximating the IOM desirable 25(OH) D level of 20 ng/ml.

This level reflects a cutoff for skeletal health in white individuals [17]. However, vitamin D insufficiency and deficiency were associated with non-skeletal disorders such as hypertension with various debated cutoff levels, depending on specific populations [18]. This is analogous to the wide

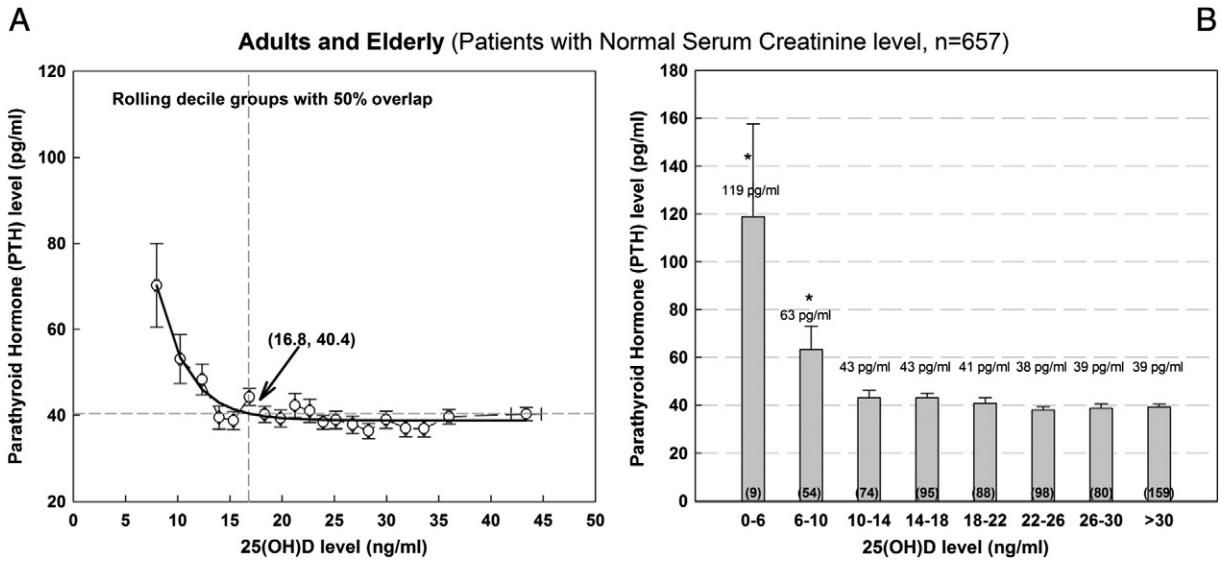

Fig. 3 – Relationship between Parathyroid Hormone (PTH) and 25(OH)D levels among adults and elderly after excluding patients with SCr above upper limit of normal. Panel A shows PTH levels as a function of increasing 25(OH)D levels. Values are expressed as means ± SE. Each data point (white circle) represents 66 patients with 50% overlap for consecutive groups, and solid black lines represent non-linear regression approximation of actual trends, for rolling decile groups as detailed in Methods. The numbers in parentheses represent the 25(OH)D at plateau and the corresponding PTH value as defined by the formula iPTH = a + b exp[c × (25(OH)D − min 25(OH)D]. Panel B shows the levels of PTH after categorizing the patients according to gradual decrements in serum 25(OH)D subgroups. Means of PTH (shown above each bar) were compared among the different groups using ANOVA and post-hoc analysis was conducted with Bonferroni correction. * Represents significant PTH difference between each of the 0–6 and 6–10 ng/ml 25(OH)D groups and the other groups (p-value < 0.05). Numbers in brackets show the actual number of patients present in each sub-group. Numbers in parentheses at arrow sign represent the mean serum 25(OH)D and PTH levels at the estimated 25(OH)D plateau (Panel A).

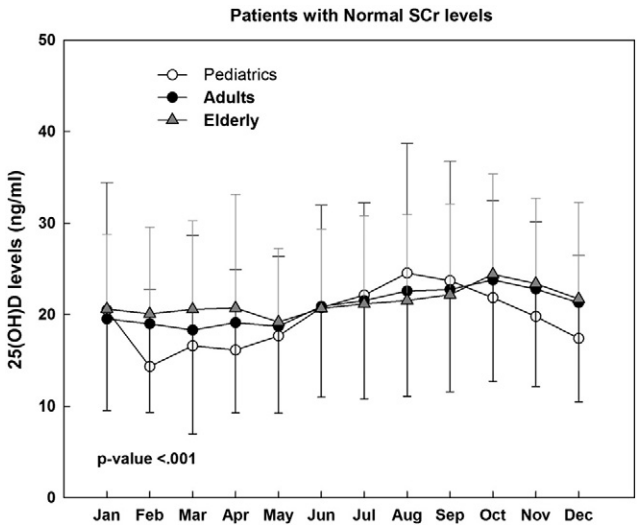

Fig. 4 – Mean levels of 25(OH)D ± SD (error bars) in pediatrics, adults, and elderly groups with normal creatinine levels, across all months. There are statistically significant monthly variations within each age group (ANOVA within each group p-value < .001) that are reflected in the lowest levels of 25(OH)D in February and highest levels in August in the pediatric age group. The number of patients per month ranged between 36 and 81 in pediatrics, 350 to 543 in adults, and 207 to 272 in elderly.

range and debated cutoff levels of/for total serum testosterone in men, i.e. 200 ng/ml for skeletal health, and higher testosterone levels for sexual health or cardiovascular disorders [19].

In the present study, the median level of 25(OH)D ranged between 14 and 17 ng/ml in girls and was lower compared to boys, where the average was closer to 19 ng/ml. These relatively low levels, and gender differences are consistent with those our group reported in two separate cohorts of apparently healthy Lebanese school adolescents [20,21] and by others in the region. These low 25(OH)D levels are also contrast with those reported in adolescents in the US NHANES III study, where mean 25(OH)D were between 26 and 36 ng/ml in over 2800 adolescents, aged 12–19 years [22]. The low mean 25(OH)D levels in the current study are reflected in the large proportion of children and adolescents having 25(OH)D levels below pre-set cut-offs, namely 58%–62% had levels below 20 ng/ml, and on the average of 85% below 30 ng/ml. Proportions varied between 55% and 74% for a cut-off of 20 ng/ml in studies in Lebanon [20], between 11% and 72% in Iran [23–25], and 39% in the study from Jordan [26]. In contrast, only 8%–29% of adolescents aged 12–19 years, had 25(OH)D < 20 ng/ml and 21%–47% had 25(OH)D < 30 ng/ml, in NHANES III [22].

Mean 25(OH)D levels ranged between 17 and 19 ng/ml in adults and elderly, and are somewhat consistent, for the most part, with reported 25(OH)D levels ranging between 10 and

12 ng/ml for studies from Lebanon, Jordan, and Iran [8]. These are in sharp contrast to those reported in a study of Iranian women, reaching a mean 25(OH) of 30 ng/ml [27], and another reporting a mean level of 73 ng/ml in Jordanian men and 40 ng/ml in Jordanian women [28]. Mean 25(OH)D value ranged between 24 and 34 ng/ml in adults from the NHANES study [22]. The low mean levels in adults and elderly from our study are reflected in the proportions of adults and elderly subjects, with 25(OH)D below 20 ng/ml, ranging between 41%–62%, and 78%–91%, for 25(OH)D below 30 ng/ml. A wide range was reported even for population based studies from Middle East. It was 95% in a study of 443 elderly Lebanese for 25(OH)D levels below 20 ng/ml [29], 43% in a study of 245 postmenopausal women in Iran [27], and only 2% in 1128 men and 14% in 3462 women studied in Jordan [28]. The proportions ranged between 23% and 99% for levels below 30 ng/ml, depending on gender and study [28–30]. In contrast, 11% to 40% of males and females (n = 2,153; >20 years) had 25(OH)D below 20 ng/ml and only 24% to 58% had 25(OH)D <25 ng/ml in NHANES III [22].

The wide range of 25(OH)D in Middle Eastern region countries [4–6,8], even in representative studies [27–29,31], may be explained by differences in clothing styles, season, gender (levels consistently lower in females than males), latitude, (18°to 48° North), education, socioeconomic status, assay used, and food fortification. In our study, the OR for a low 25(OH)D level was independently predicted by age, gender, season, patient service status, and study time period. The systematic increase in mean 25(OH)D levels in our study between the two time periods, and in adult and elderly female subjects, may possibly reflect an increased osteoporosis awareness within the medical profession and the public in light of the dissemination of the first Lebanese Practice Guidelines for Osteoporosis Assessment and treatment in 2002 [32] and the first Update in 2007 [33], both of which underscored calcium and vitamin D recommendations. This is also reflected in the larger number of vitamin D assays requested in the latter 2 years (N = 4350) compared to that in 4 years (N = 5704), and the higher 25(OH) levels in women than men, a subgroup particularly targeted in awareness campaigns worldwide. However, a difference due to a change in assays, in the middle of the first time period, cannot be excluded. Despite the fact that the sun shines over 300 days per year in our country, the lowest levels registered in the winter across all age groups reflect the shorter day, and the lower sun exposure in this season due to school and/or colder weather. Vitamin D predictors identified here-in have been previously demonstrated in other studies from the region, with the exception of an inverse seasonal pattern in gulf countries due to the scorching heat in summer [4,6,34]. Additional predictors identified in studies from Asia, Europe, and the US include sun exposure, skin pigmentation, air pollution, consumption of fatty fish, cod liver oil, margarine, exercise, physical performance score, and physician counseling [5,34]. In light of the high prevalence of hypovitaminosis D in apparently healthy individuals, current guidelines do not recommend routine screen of vitamin D, and reserve testing to high risk individuals, which is supported by our data [12,35].

Using regression analyses, the plateau, which is the 25(OH)D level above which PTH levels did not decrease any further, was 16.8 ng/ml in the overall group and 16.1 ng/ml in females with normal SCr and was slightly higher but below 21 ng/ml when including subjects with mild increments in SCr. Our findings are quite consistent with results from a recent study that defined a plateau of 18.5 ng/ml using a computerized laboratory database of 13,373 subjects partaking in a health maintenance organization in Israel [36]. The values proposed for plateau in the literature vary widely between 16 and 60 ng/ml [14,37–43]. Such variation is in part explained by differences in ethnicity, age, gender, renal function status, assay used, and most importantly the method used to implement curve fitting and derive plateau. Using a large database, our population specific plateau is between 17 and 21 ng/ml, closely approximating the IOM desirable level (13). Based on the 25(OH)D–PTH relationship a desirable 25(OH)D level would be 20 ng/ml in Lebanese subjects. On the other hand, the cross sectional analysis of the National Health and Nutrition Examination Survey (NHANES) 2003–2006, performed on 14681 subjects ages ≥ 6 years shows that optimal 25(OH)D status, defined by estimated maximum PTH suppression, doesn't occur until at least 25(OH)D level is ≥40 ng/ml, which is higher than our population specific plateau [44]. It is important to note that desirable 25(OH)D levels derived from the 25(OH)D–PTH relationship have varied widely between studies [45]. This may in part be explained by the fact that the relationship is modulated by calcium intake, and possibly age and menopausal status, variables that all affect calcium absorption. We did not have the possibility of assessing calcium in our study.

On the average, almost half of the subjects in this study fall below such cut-off, across all age groups and genders. In view of the above, and the mean 25(OH)D levels reported here-in, it is anticipated that the vitamin D doses recommended by the IOM, which is 600 IU/day, as recommended for the pediatric age group and adults, would on average be anticipated to raise mean 25(OH)D levels by only 6 ng/ml, (assuming a 1 ng/ml increase in 25(OH)D for each 100 IU of vitamin D), and would thus fall short of ensuring that 97% of the Lebanese will be above such desirable level. For example, in female children, the median would rise from 14 ng/ml to 20 ng/ml, and thus only 50% and not 97% of such group would reach the putative desirable level recommended by the IOM. Moreover, for females adults, the mean of 25(OH)D would rise from 18.9 to 24.9 ± 10.7 ng/ml, assuming the same standard deviation. Therefore, according to the definition of Gaussian/normal distribution, around 84% of the population would then have 25(OH)D levels > 14.2 ng/ml (mean –1 SD). A level of 19.5 ng/ml or more, representing the mean (24.9 ng/ml) – 0.5 SD (5.35 ng/ml) can be reached by only 69.1 % of the population. The proportions of subjects above the putative desirable level would be even lower, if one chose a desirable 25(OH)D range above 30 ng/ml, to account for variations in assays, differences between genders and seasons, and the fact that the plateau derived from group data only represent mean values that do not reflect individual variations around such mean.

Limitations of our study include its cross-sectional, non population-based nature, the use of SCr values rather than the GFR (or CKD-EPI/MDRD formula) as an index of kidney function, due to the lack of data needed to derive such parameter. Other limitations are the small sample size for the

pediatric group, the fact that data points may not all be independent, and the study included more women than men. Another limitation is the lack of data on BMI or other measures of fat content, the latter a major determinant of 25 (OH)D. In Lebanon, Sibai et al. reported in the first national population-based epidemiological study (n = 2104 subjects) that 66%–70% of subjects, aged 60 years and above, are overweight (BMI ≥ 25 kg/m_2) and 26%–30% are obese (BMI ≥ 30.0 kg/m^2) [46]. This was similar to WHO reports where 61.8% of the Lebanese population are overweight (66.1% were men) and 27.4% are obese (25.8% were men) [http://www.who.int/mediacentre/factsheets/fs311/en/]. Updated data on Lebanese elderly were published in 2012 by Nasreddine et al. who highlighted an alarming increase of mean BMI between 2 time periods (1997 and 2009) from 17.4% to 28.2% with Odd ratio (OR) = 2.01 (95% CI,1.67–2.43) [47].

We, however, believe the results to be representative of findings in the Lebanese population at large, in view of the comparable mean 25(OH)D values to those reported by our group in two studies conducted in apparently healthy school children and one in a population based study of elderly ambulatory subjects [20,21,29]. They are also further validated by similar results obtained in a population based study conducted in the same study period in Lebanon, using the same 25(OH)D assay [48]. Furthermore, it capitalizes on a very large database from a referral academic center, drawing patients from all parts of the country, that included a wide age span evaluated within same point of care, and using, for the most part, the same 25(OH)D assay, over a period of 8 years. However, because of the nature of the database, the study could not unravel other predictors of low 25(OH)D levels, including hydroxylation polymorphisms [49], body mass index, medical conditions, medications, and lifestyle factors such as veiling.

This large scale study unequivocally demonstrates the high prevalence of hypovitaminosis D, and underscores its most robust predictors, in a sunny country in the Middle East, predictors easily identified in clinical practice. This high prevalence is consistent, whether one relied on the IOM recommended desirable vitamin D level, or a population specific cut-off, and implies that higher doses than currently recommended would be needed to reach country specific "desirable" levels. The same is likely to apply to many other Middle Eastern and Asian populations at particular risk of hypovitaminosis D, and thus the need to develop country-specific recommendations in term of desirable ranges for vitamin D levels and doses needed to reach them.

Authors' roles

Study conception and design, responsibility for data integrity: Dr. Ghada El Hajj Fuleihan. Study conduct and data collection: Dr. Cynthia Yazbeck, Ms. Tala Ghalayini and Dr. Maha Hoteit. Data acquisition and analysis: Mrs. Laila Al Shaar, Ms. Maria Bou Sleiman, Dr. Cynthia Yazbeck, Dr. Maha Hoteit and Dr. Ghada El-Hajj Fuleihan. Data interpretation: Dr. Maha Hoteit, Mrs. Laila Al Shaar, and Dr. Ghada El-Hajj Fuleihan. Drafting manuscript: Dr. Maha Hoteit, Mrs. Laila Al Shaar and Dr. Ghada El Hajj Fuleihan. Revising manuscript content and approving final version of manuscript: all authors.

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Declaration of interest

The authors declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2014.04.009.

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