Vitamin D deficiency in Spain: a population-based cohort study

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Running tittle: Population-based vitamin D values in Spain

ABSTRACT

Background: Vitamin D deficiency is common worldwide.No homogenous reference values have yet been established and no studies of values have been done in Spain involving a large number of participants.

Objective: To study the population concentrations of vitamin D in a representative sample of the Spanish population.

Subjects/Methods: The study involved two cohorts from Spain,the Asturias Study and the Pizarra Study,which are two prospective,population-based studies involving 2260 participants.In 1262 subjects (age: 20-83 years) we studied 25-hydroxyvitamin D,intact parathyroid hormone (iPTH),calcium,phosphorus and creatinine.

Results: The median population values of 25-hydroxyvitamin D and iPTH were 22.46 ng/mL and 42.29 pg/mL,respectively.The values of 25-hydroxyvitamin D were significantly higher in summer and correlated with age (beta=-0.05±0.01,$p<0.0001$),creatinine (beta=6.42±1.17,$p<0.0001$),and iPTH (-0.07±0.01,$p<0.0001$),but not with calcium,phosphorus or sex.The increase in iPTH with age was seen whatever the values of 25-hydroxyvitamin D,and was greater in the older persons.The concentration of iPTH rose continuously with effect from 25-hydroxyvitamin D values below ≈30 ng/mL.Values above ≈35 ng/mL were associated with a significantly lower concentration of iPTH.

Conclusions: One third (33.9%) of the Spanish population may be at risk for Vitamin D deficiency.25-hydroxyvitamin D values above 30 ng/mL can safely discard “hyper PTH”.The increase in iPTH concentration is greater in older persons for similar values of 25-hydroxyvitamin D.

Keywords: Vitamin D deficiency.

INTRODUCTION

Previtamin D is synthesized in the skin after sun exposure and can also be ingested with foods having high concentrations of vitamin D.Previtamin D is metabolized in the liver to 25-hydroxyvitamin D and converted in the kidney to the active form 1,25-dihydroxyvitamin D (Dusso et al.,2005;Holick,2007).

Vitamin D deficiency can cause a decrease in bone mineral density,secondary hyperparathyroidism and osteomalacia,and it has also recently been associated with numerous other disorders,such as cancer,cancer,diabetes,hypertension,and autoimmune diseases (Holick,2010).

Vitamin D deficiency is common,though its prevalence varies depending on the characteristics of the study population (Adami et al,2009;Annweiler et al.,2009; Bouuaert et al.,2008;Carnevalle et al.,2001;Hintzpeter et al.,2008;Hintzpeter et al.,2008; Hypponen et al.,2007;Isaia et al.,2003; Lips,2010;Zittermann et al.,2009)

Despite numerous studies,the reference values of 25-hydroxyvitamin D have not yet been definitively established,and various different cut-off levels have been proposed for the criterion for vitamin D deficiency.A recent consensus document (Henry et al 2010) concluded that the minimum desirable concentration of 25-hydroxyvitamin D should be 20-25 ng/mL.

The nutritional deficiency of vitamin D is generally studied by measuring the reserves of vitamin D according to the concentration of 25-hydroxyvitamin D (Holick,2010),either alone or else combined with the measurement of parathyroid hormone (iPTH).

Even though Spain is a country with many hours of sunshine,most studies in Spain show a high prevalence of vitamin D deficiency.However,many of these studies have included persons aged 65 years or over,frequently institutionalized persons

(thus,not representative of the general population and with different rates of sun exposure,activity and diet),or else involved only a few persons,with the largest study in the last ten years in the general population (Mata–Granados et al.,2008) including just 215 persons.Thus,no representative studies involving a large sample of healthy persons have been carried out in Spain.The mean levels of 25-hydroxyvitamin D in middle aged people range from 14-25.9 ng/mL,with 26% to 85.1% of persons having values below 20 ng/ml (Calatayud et al.,2009;González Solanellas et al.,2008;Mata-Granados et al.,2008).In persons aged 60 years or more,the mean 25-hydroxyvitamin D concentration is even lower: 6.95-17 ng/ml,with 46.4% to 85% having values below 20 ng/ml (Gomez-Alonso et al.,2003;Niño Martín et al.,2008 ; Pérez-Llamas et al.,2008;Rodríguez Sangrador et al.,2008;Vaquero et al.,2004).

There is a well defined negative correlation between iPTH and 25-hydroxyvitamin D (Chapuy et al.,1997;Cristensen et al.2010;Ho-Pham et al.,2010; Khosla et al.,1997;Leboff et al.,1999; Malaban et al.,1998;Thomas et al.,1998;Vieth et al,2003;von Muhlen.,2005),but the features of this relation and the influence of age have not been fully defined.iPTH seems to be higher in older people than in young people (Arabi et al.,2010;Christensen et al.,2010),but it has been suggested that the relationship between Vitamin D and iPTH is different in older persons compared to young persons,such that for the same levels of 25-hydroxyvitamin D older persons could have higher iPTH (Arabi et al.,2010;Vieth et al.,2003)

The aims of this study were,firstly,to examine the values of 25-hydroxyvitamin D in a representative sample of the Spanish population and,secondly,to examine the influence of age in the relation between 25-hydroxyvitamin D and iPTH.

SUBJECTS AND METHODS

Study sample

The study was carried out in two population-based cohorts,one in the north and the other in the south of Spain,both studied at the same time and using similar methods.The study populations and the design of these two surveys have been described previously (Soriguer et al.,2002;Soriguer et al.,2008;Valdes et al.,2007).The Asturias Study is a prospective,population-based survey of diabetes and cardiovascular risk factors.The baseline examination was carried out during 1998-1999,when 1034 individuals were randomly selected to determine the prevalence of diabetes and prediabetes in the region of Asturias (northern Spain).In 2004-2005,these same subjects were invited for a follow-up examination,700 of whom accepted (Valdes et al.,2007).The Pizarra study is a population-based prospective study undertaken in a population from Andalusia,southern Spain.The first phase of the study (1996-1998) included 1226 individuals,selected randomly from the municipal register of Pizarra,Malaga,Spain.Of the original cohort,784 persons were reassessed in 2002-2004 (Soriguer et al.,2002;Soriguer et al.,2008).The final sample size was 1484 persons:700 from Asturias,784 from Pizarra).

Persons were excluded from the study if they were institutionalized,had chronic disorders that could affect phosphocalcium metabolism,or if their creatinine was greater than 1.9 mg/dL,calcium >10.9 mg/dL or phosphorus <2.5 mg/dL.Thus,the total number of persons finally studied was 1262.

All the participants completed a clinical survey and underwent an anthropometric study,as well as providing a venous blood sample that was centrifuged at the time of study and the plasma separated and frozen at –80ºC until later analysis.In

both cohorts measurements were made simultaneously of 25-hydroxyvitamin D,iPTH,calcium,phosphorous and creatinine in the same laboratory.

The 25-hydroxyvitamin D was measured by electrochemoluminiscence(ECLIA immunoassay,Modular Analytics E170®,Roche).The value is given in ng/mL.The analytical sensitivity was 4-100 ng/mL.Analytical coefficient of variation (CV):7.3%

iPTH was measured by electrochemoluminescence(ECLIA immunoassay,Modular Analytics E170®,Roche).The value is given in pg/mL.The assay sensitivity was 1.20-5000 pg/mL.Analytical CV:7.02%.Normal values in our laboratory are:15-60 pg/mL.

The creatinine was measured by spectrophotometry (Dimension Vista®,Siemens).The value is given in mg/dL.Sensitivity was 0.1-20 mg/dL.Analytical CV:2.7%.

The calcium was measured by spectrophotometry (Dimension Vista®,Siemens).The value is given in mg/dL.The sensitivity was 5-15 mg/dL.Analytical CV:3.7%.

The phosphorus was measured by spectrophotometry(Dimension Vista® System,Siemens).The value is given in mg/dL (conversion factor: mg/dL x 0.323 = mmol/L).The sensitivity was 0.1-9 mg/dL and the analytical CV was 4.8%.

The solar radiation was measured in watts per square meter(W/m^2).The data were obtained from the official information provided by the national meteorological stations.To transform the units into Joules per square meter($Joules/m^2$),the power in W/m^2 should be multiplied by 86,400(seconds in a day).

The project was approved by the ethics committees of Carlos Haya Hospital in Malaga and the Hospital Central in Asturias.

Statistical analysis

The continuous variables are presented as the mean and standard deviation or percentiles and the classification variables as proportions.Adjustment of the variables to normality was done with the Shapiro test.The statistical difference between the means of the continuous variables was calculated with the ANOVA test for one or more ways,and for the qualitative variables with the Chi^2test.

The correlation between variables was measured by calculating the linear coefficient of correlation (Pearson's r) and the regression by designing multiple linear regression models.

The most suitable cut-off point to identify the population reference value of 25-hydroxyvitamin D was calculated by designing ROC curves and calculating the positive and negative predictive value(PPV and NPV).

The strength of association between two variables,adjusted for third variables,was measured using the Odds Ratio (OR),calculated from the coefficient of a logistic regression model.In all cases the level of rejection of a null hypothesis was set at α=0.05 for two tails.(In all models sex was coded as male=0 and female=1)

RESULTS

The mean age of the study participants was 50.3±14.4 years(range:20-83 years),with 57% women and 43% men.The median 25-hydroxyvitamin D and iPTH concentrations were 22.46 ng/mL and 42.29 pg/mL,respectively.Table 1 summarizes the population distribution by percentiles of 25-hydroxyvitamin D,creatinine, iPTH,calcium and phosphorus.

As the age increased,the concentration of 25-hydroxyvitamin D fell ($p<0.0001$) and that of iPTH rose ($p<0.0001$),after adjusting for sex,plasma creatinine,individual

study (Asturias or Pizarra) and the month of blood extraction (Figure 1).In both men and women the plasma creatinine concentration rose significantly with age,after adjusting for the particular study and the study month ($p<0.0001$) ($R^2=0.43$,$p<0.001$).The concentration of plasma calcium did not change significantly with age(Data not shown).

The values of 25-hydroxyvitamin D were significantly higher in the summer months in both cohorts ($P<0.0001$,adjusted for age,sex and creatinine),months that coincide with greater sunlight (Figure 2).In summer,the proportion of persons with 25-hydroxyvitamin D levels >30 ng/mL was greater than in spring or winter: 23.3%,12.8% and 9.3%,respectively ($p<0.001$ after adjusting the logistic model for age,creatinine,sex and the individual study).The proportion of persons with 25-hydroxyvitamin D values <20 ng/mL was higher in winter than in spring or summer: 37.2%,34.4% and 26.5%,respectively ($p<0.001$ after adjusting the logistic model for age,creatinine,sex and the individual study).

The values of 25-hydroxyvitamin D rose as the plasma creatinine levels increased,after adjusting for age ($p<0.001$) and iPTH ($p<0.0001$).

The values of 25-hydroxyvitamin D were significantly lower in the Pizarra Study than in the Asturias Study (22.75±6.23 ng/mL vs.23.75±7.17 ng/L,$p=0.01$).In parallel,the values of iPTH were significantly higher in Pizarra than in Asturias (47.00±19.22 pg/mL vs.44.67±16.69 pg/mL; $p=0.02$).

The concentration of 25-hydroxyvitamin D,iPTH and calcium did not differ significantly depending on sex after adjusting the contrast hypothesis for age and the individual study(data not shown).

A multiple linear regression model showed that the concentration of 25-hydroxyvitamin D correlated significantly with age (beta=-

0.03±0.01,p<0.0001),plasma creatinine(beta=6.66±1.17,p<0.0001) iPTH(-0.07±0.01,p<0.0001),and body mass index (BMI) (-0.14±0.03,p<0.000) but not with calcium,phosphorus or sex.The full model explained 8.3% of the variance in the values of 25-hydroxyvitamin D (p<0.0001).

In a multiple linear regression model the iPTH correlated significantly with age (beta=0.27±1.15; p<0.0001),sex(beta=4.07±1.15; p<0.0001),25-hydroxyvitamin D (beta=-0.45±0.07,p<0.0001),plasma creatinine(beta=6.08±3.01,p=0.02),phosphorus(-4.90±1.00,p<0.0001),and BMI(0.32±0.09, p<0.001) but not with calcium.The full model explained 14% of the variance in iPTH(p<0.0001).

In a multiple linear regression model the levels of phosphorus correlated significantly with age (beta=-0.002±0.001,p=0.05),sex (beta=0.22±0.03,p<0.0001),calcium (beta=0.18±0.03,p<0.0001),creatinine(beta=0.17±0.08,p=0.06),and iPTH (beta=-0.004±0.001,p<0.0001) but not with 25-hydroxyvitamin D or BMI.

The increase in iPTH with age was seen whatever the values of 25-hydroxyvitamin D,and were greater in older persons (Figure 3).

Table 2 summarizes the sensitivity,specificity,PPV and NPV,considering the iPTH value (>60 pg/mL) as the biological reference criterion of hypovitaminosis D,for different cut-off values of 25-hydroxyvitamin D.The iPTH levels rose continuously with effect from 25-hydroxyvitamin D values lower than ≈30 ng/mL.Values above ≈35 ng/mL were associated with significantly lower levels of iPTH (Figure 4).

The area under the ROC curve (25-hydroxyvitamin D value according to iPTH) was 0.62±0.021(95% CI,0.58-0.66)(p<0.0001)

Logistic regression models: The variable best predicting concentrations of 25-hydroxyvitamin D below 20 ng/mL was the value of plasma creatinine(Beta:-1.66;OR

0.19;p<0.0001),followed by the value of iPTH.Inclusion in the model as a dependent variable of another different cut-off point for iPTH (≤65 pg/mL) did not change substantially the strength of the prediction.The variables most strongly associated with values of iPTH (<=60 or >60 pg/mL) were plasma phosphorus (Beta:-0.77; OR:0.46; p<0.0001) and 25-hydroxyvitamin D (Beta:0.53; OR:1.70;p=0.001).

DISCUSSION

If we use the reference value of 20 ng/mL,33.9% of the Spanish population are at risk for vitamin D deficiency,with no significant differences between the study in the north and the study in the south (prevalences of 31.3% and 35.0% respectively).Several studies have been undertaken in Spain on the vitamin D nutritional situation,especially during the 1990s.Most of these studies coincided concerning the presence of vitamin D deficiency,but the prevalence figures for the deficit varied,probably because most were done with opportune or institutionalized samples,and generally involved a low number of persons (Calatayud et al.,2009;Gomez-Alonso et al.,2003;González-Solanellas et al.,2008;Mata-Granados et al.,2008;Pérez-Llamas et al.,2008;Vaquero et al.,2004).In other countries in Europe,the percentages of deficiency and insufficiency vary (Lips,2010).Italy has prevalence levels of 17% below 12 ng/ml in winter in the south (Carnevalle et al,2001) and one third of healthy women below 20 ng/ml in the north (Adami et al,2009),which is very similar to our prevalence.Germany has lower levels of vitamin D than in our study: the prevalence of vitamin D insufficiency in the German National Health Interview and Examination Survey was more than 50% in the general population and 60% in children (Hintzpeter et al.,2008;Hitzpeter et al.,2008),with the DEVID (The vitamin in Deutschland) study reporting mean levels of 41±22 nmol/L (Zittermann et al.,2009).In the British population,the prevalence is greater than in Spain:

Hypponen et al reported a prevalence of hypovitaminosis D <75 nmol/L in 87.1% of participants in winter and in 60.9% in summer (Hypponen et al.,2007).In elderly people,the prevalence of hypovitaminosis D in France,Belgium,Italy and other countries is more than 60% (Annweiler et al.,2009;Bouuaert et al.,2008;Isaia et al.,2003).

In agreement with other studies,we found a negative correlation between levels of 25-hydroxyvitamin D and iPTH (Adami et al.,2010;Arabi et al.2010;Christensen et al,2010;Ho pham et al.,2010).On the other hand,the variability in iPTH with seasonal climate changes was lower than that for 25-hydroxyvitamin D,as occurred elsewhere (von Muhlen et al.,2005) and the correlation between iPTH and 25-hydroxyvitamin D was less obvious in spring and summer (data not shown),as in other studies (Maeda et al.,2010),probably related with the different turnover of vitamin D3 and iPTH at a time when the production of vitamin D3 in the skin is greater.In general,most studies assume that iPTH reaches a plateau when 25-hydroxyvitamin D values reach a particular concentration (Chapuy et al.,1997;Khosla et al.,1997;Leboff et al.,1999;Malaban et al.,1998;Thomas et al.,1998; von Muhlen et al.,2005).This observation has led to the use of iPTH levels as a biological marker for the nutritional status of vitamin D(Holick,2007).Others have found no plateau concerning iPTH vs.25-hydroxyvitamin D,suggesting that the choice of an optimum or desirable concentration of 25-hydroxyvitamin D,as based solely on iPTH,could be arbitrary (Vieth et al,2003;Ho-Pham et al,2010).Some studies have used linear or exponential models to predict the cut-off point of 25-hydroxyvitamin D values above which the iPTH concentration becomes stable (Chapuy et al.,1997).In our study the 25-hydroxyvitamin D*iPTH plot was very similar to that reported by others (Vieth et al.,2003).However,despite the high level of statistical significance of the various mathematical adjustments,none of the mathematical models used explain more than about 5% of the variance in iPTH (data

not shown).In our study,using the cut-off values suggested in the ROC curve,we calculated the predictive values of “hyper iPTH” using various different cut-off points of 25-hydroxyvitamin D.A 25-hydroxyvitamin D cut-off point of ≤30 ng/mL was able to diagnose “hyper iPTH” with a low degree of certainty (18.1%),whereas 25-hydroxyvitamin D concentrations above 30 ng/mL were associated with a high degree of certainty (92.8%) at discarding “hyper iPTH”.

In our study,as in others,the levels of 25-hydroxyvitamin D fell with age,at the same time as the iPTH increased (Arabi et al 2010.;Vieth et al.,2003) and the phosphorus decreased.Only a few studies have examined the effect of age and kidney function on turnover of 25-hydroxyvitamin D (Vieth et al.,2003;Cristensen et al.;2010).In our study,age and plasma creatinine were closely related ($r=0.25, p<0.0001$) and the levels of 25-hydroxyvitamin D correlated positively with the plasma creatinine,independently of the iPTH levels.In the study by Vieth (Vieth et al.,2003),the correlation between age and creatinine was just seen in the older persons,the correlation between 25-hydroxyvitamin D and creatinine only in the younger persons and the change in iPTH correlated with the creatinine only in the older persons,not the younger.Von Mulhen (von Mulhen et al.,2005) on the other hand,found no correlation between creatinine clearance and levels of iPTH or vitamin D.Although most reports have documented a vitamin D deficiency in uremic patients especially due to chronic kidney disease related comorbidities (LaClair et al.,2005 ; Mehrotra et al.,2008),other have not (Craver et al.,2007).Indeed,25-hydroxyvitamin D levels remained unchanged and levels of 1,25-dihydroxyvitamin D fell as the kidney disease progressed.In another study in patients with normal renal function,levels of vitamin D3 correlated positively with the creatinine (Vieth et al.,2003),as they did in our study.We do not have an easy explanation for this issue.It is plausible that a slight impaired renal function may be

associated with a lower production of 1-25-hydroxyvitamin D,which induces an increase in iPTH values.The fact that iPTH levels correlated with serum creatinine in our study independently of vitamin D levels,supports this argument.Lastly,we only included patients without chronic clinical disorders but with many hours of sunshine exposure,which may also contribute to maintenance stable 25-hydroxyvitamin D levels,even in presence of slight renal failure.Further studies are needed to clarify this concern.

The fall in 25-hydroxyvitamin D with age seen in this study seems consistent with the findings of others (Arabi et al.2010;Chapuy et al.,1997;Jacques et al.,1997; Malabanan et al.,1998;Mezquita Raya et al.,2001 ;Von Muhlen.et al.,2005;Vieth et al.,2003),though not all (Christensen et al.,2010 ; Harris et al.,2000; Tangpricha et al.,2002;).The rise in iPTH levels with age seems to occur whatever the levels of 25-hydroxyvitamin D and does not seem to be explained just by the vitamin D3 nutritional status.These results have also been found by others (Vieth et al.,2003;Arabi et al.;2010).It seems,therefore,that aging is accompanied by a reduction in the production by the skin of vitamin D3 (MacLaughlin et al.,1985) together with some form of resistance to the effects of 25-hydroxyvitamin D,as has also been seen in older persons for 1,25-hydroxyvitamin D (Pattanaungkul et al.,2000) and proposed by others (Vieth et al.,2003).These reasons,together with the reduction in gut absortion of vitamin D in older persons (Bhutto et al.,2008),may contribute to the changes in levels of 25-hydroxyvitamin D and iPTH with age.

If we use a concentration of 25-hydroxyvitamin D as a criterion for nutritional deficiency,e.g.,≤20 ng/mL,those persons studied in summer,spring and winter had a prevalence of vitamin D3 deficiency of 26.9%,34.5% and 37.2%,respectively (p=0.01).However,if we use iPTH ≤60 pg/mL,the prevalence of nutritional deficiency

was 15.8%,19.9% and 19.8%,respectively,with no significant differences between seasons.Using the measurement of both 25-hydroxyvitamin D and iPTH,though,did not substantially improve the discriminative capacity,as although 61.6% of the persons studied in summer had simultaneous high concentrations of 25-hydroxyvitamin D and iPTH ≤60 pg/mL,only 8.9% of those studied in winter had low concentrations of 25-hydroxyvitamin D and high levels of iPTH.The results of this study carried out in a representative Spanish population show the difficulties involved in establishing with precision a diagnosis of the nutritional status of vitamin D by measuring the concentrations of 25-hydroxyvitamin D and iPTH.

At this time the aims of an adequate nutritional supplement with vitamin D should be to reach a sufficient concentration of 25-hydroxyvitamin D to achieve levels of iPTH ≤60 pg/mL.However,with the simultaneous measurement of 25-hydroxyvitamin D and iPTH the validation of this objective is far from being satisfactorily achieved.Nonetheless,our results suggest,like others (Heaney et al.,2000;von Muhlen et al.,2005),that values of 25-hydroxyvitamin D above 30 ng/mL could prevent secondary hyperparathyroidism in most persons.Even so,numerous gaps still remain concerning the best criterion for the diagnosis of vitamin D deficiency.Future prospective studies with large series of populations would therefore appear necessary,using clinical and risk prevention criteria to identify the most suitable criteria to define vitamin D deficiency.

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Table 1: Population distribution of the levels of 25-hydroxyvitamin D,creatinine,iPTH,calcium and phosphorus

	Percentiles						
	5	10	25	50	75	90	95
25-hydroxyvitamin D (ng/mL)	13.58	15.41	18.56	22.46	26.97	31.11	34.69
Creatinine(mg/dl) (Male)	0,7	0,7	0,8	0,9	1	1,1	1,2
Creatinine(mg/dl) (Female)	0,5	0,5	0,6	0,7	0,8	0,9	0,9
iPTH (pg/mL)	23.83	26.76	33.10	42.29	54.75	69.04	78.95
Ca (mg/dL)	8.70	8.90	9.10	9.40	9.60	9.90	10.10
P (mg/dL)	2.70	2.90	3.20	3.50	3.80	4.10	4.30

Data are expresed in percentiles.

Table 2: Selection criteria for the cut-off point of 25-hydroxyvitamin D using iPTH >60 pg/mL as the reference value

25-hydroxyvitamin D	(Se)	(Sp)	(PPV)	(NPV)
<=10 ng/mL	54.5	83.6	2.81	99.5
<=20 ng/mL	23.9	87.1	48.8	68.9
<=25 ng/mL	19.9	89.9	78.4	37.1
<=30 ng/mL	18.1	92.8	94.3	14.6
<=35 ng/mL	17.1	96.3	99.1	5.0 %

Sensitivity (Se) = P(iPTH high/25-hydroxyvitamin D below the cut-off point); Specificity (Sp) = P(iPTH normal/25-hydroxyvitamin D above the cut-off point); PPV: P(25-hydroxyvitamin D below the cut-off point /iPTH high and NPV: P(25-hydroxyvitamin D above the cut-off point /iPTH normal).

Legends to the figures

Figure 1: Concentrations of 25-hydroxyvitamin D (a)

● Pizarra

♦ Asturias

Figure 2: Plasma concentration of 25-hydroxyvitamin D and iPTH according to the mean daily radiation.

Figure 3: Concentration of iPTH according to age intervals and values of 25-hydroxyvitamin D

Figure 4: Concentration of iPTH according to levels of 25-hydroxyvitamin D.

Figure 1

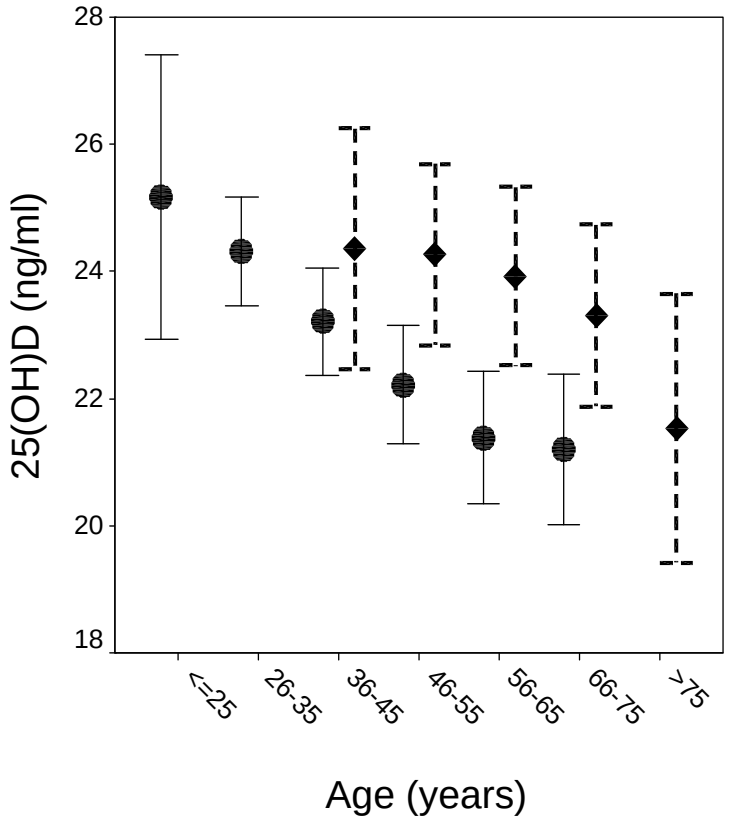

28
26
24
22
20
18
25(OH)D (ng/ml)
<=25
26-35
36-45
46-55
56-65
66-75
>75
Age (years)

Figure 2

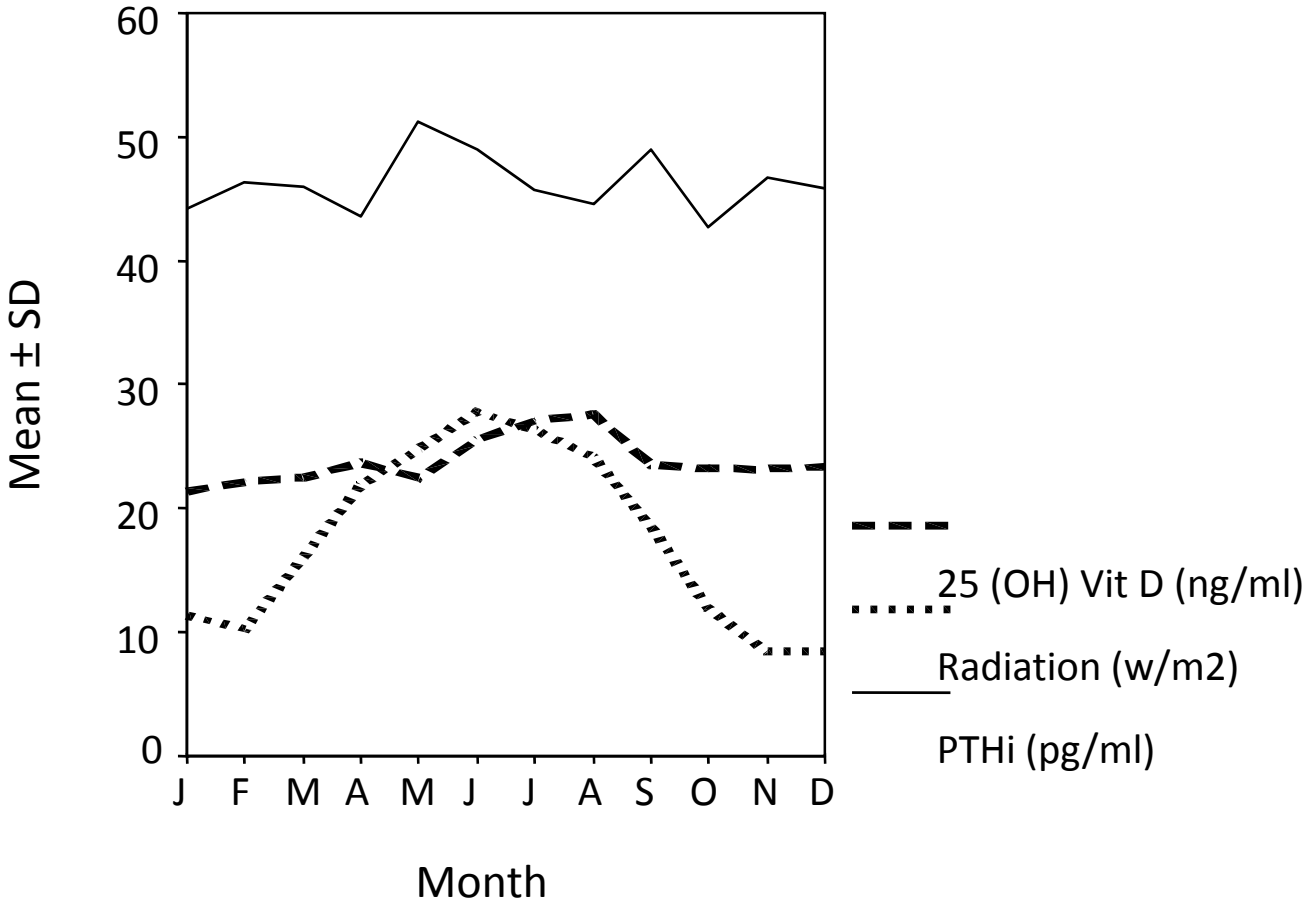

60
50
40
30
20
10
0
Mean ± SD
J F M A M J J A S O N D
Month
25 (OH) Vit D (ng/ml)
Radiation (w/m2)
PTHi (pg/ml)

Figure 3

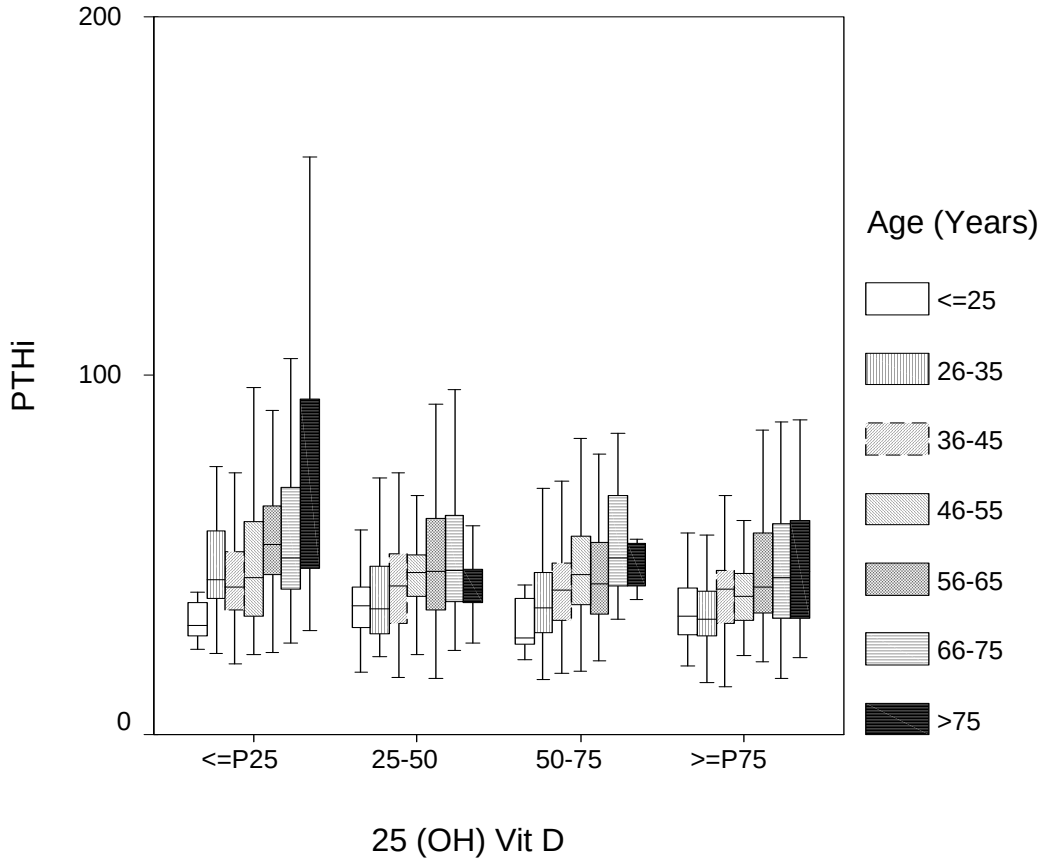
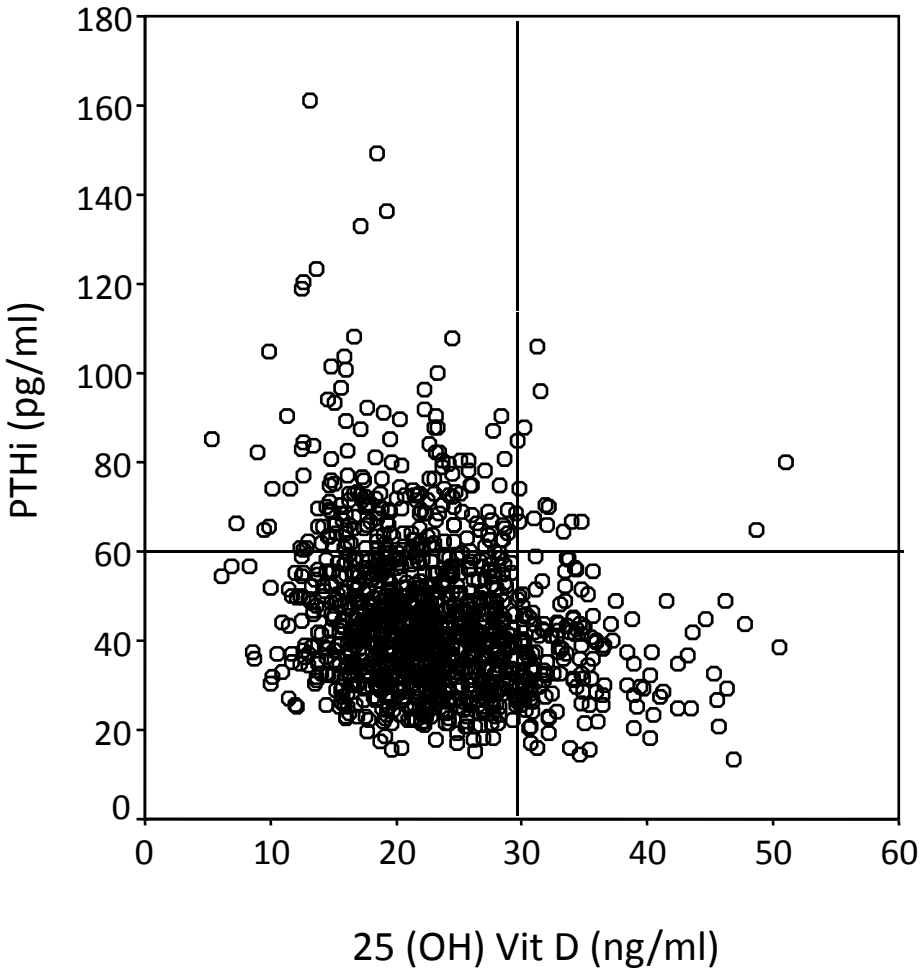

200
100
0
PTHi
<=P25
25-50
50-75
>=P75
25 (OH) Vit D
Age (Years)
<=25
26-35
36-45
46-55
56-65
66-75
>75

Figure 4


180
160
140
120
100
80
60
40
20
0
PTHi (pg/ml)
0
10
20
30
40
50
60
25 (OH) Vit D (ng/ml)