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VITAMIN D DEFICIENCY/INSUFFICIENCY AND OBESITY AND METABOLIC DISORDERS IN COMMUNITY-LIVING CHILEAN ELDERLY PEOPLE

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Abstract: *Background: Objective:* To examine obesity and metabolic disorders associated with vitamin D (VitD) deficiency/insufficiency in community-living Chilean older people. *Methods:* Cross sectional study in 1186 community dwelling subjects 60-98 years old (807 women) residing in Santiago Chile. Plasma levels of 25-hydroxyvitamin D (25(OH)D) were determined by radioimmunoassay. Glucose, insulin and US-CRP, were measured in a fasting blood sample. Blood pressure and complete anthropometry were evaluated. Diabetes was defined as ≥ 126 mg/dl or use of anti-diabetic agents, fasting glucose intolerance (FGI) was defined as glucose ≥100 mg/dL and insulin resistance as HOMA-IR ≥ 2.6. VitD deficiency was defined as a serum 25(OH)D concentration <50 nmol/L and VitD insufficiency as 50-74 nmol/L. The relationship between VitD and metabolic disorders was studied using multivariable logistic regression models. *Results:* Mean serum 25(OH)D was 63.2 nmol/L ± 33.1 (men 66.0 ± 33.0; women 62.0 ± 33.2, p=0.48) the lowest in people ≥70 years (55.8 ± 26.6). VitD levels were under 75nmol/L in 67.0% of men and 73.0% of women (p=0.020). The prevalence of VitD deficiency was 36.5% in men and more prevalent in women 40.8% (p=0.045). Obesity was present in 37.6% of women and 26.3% of men p<0.001. Significant negative crude association between VitD across BMI categories was found in the total sample (p<0.001). Crude association of VitD <50nmol/L with obesity (p=0.002), waist circumference (p=0.011), Insulin resistance (p<0.001), Metabolic syndrome (p=0.004), HTA (p<0.001) and Age ≥ 70 years (p<0.001) was observed. After adjustment by age, sex, waist circumference and season, VitD <50nmol/L was associated with increased risk of insulin resistance, OR 3.12 (95%CI 1.66 – 5.86), p<0.001. *Conclusion:* High prevalence of VitD deficiency/insufficiency was observed in the Chilean older people. VitD deficiency is associated with insulin resistance. In the future, randomized controlled trials are needed to establish a cause-effect relationship between VitD deficiency, obesity and its metabolic consequences.

Key words: Vitamin D, vitamin D deficiency- insufficiency, obesity, metabolic disorders.

Introduction

Vitamin D increases intestinal absorption of calcium and phosphorus intake and improve calcium reabsorption by the kidney, leading to the elevation of both minerals in the plasma (1). Consequently, The major biological actions of vitamin D are the maintenance and regulation of mineral homeostasis of bone remodelling (2, 3). However multiple other actions it has been described (4). Among those one of the most important is its role in glucose metabolism (5). It has been observed in vitro and animal studies that vitamin D may play a role in glucose homeostasis through its effect on the synthesis, secretion and insulin sensitivity (6, 7). Different studies have reported negative association between vitamin D and risk of diabetes mellitus (5, 8, 9), insulin resistance (10), altered blood pressure (11) and metabolic syndrome (12).

Only a small amount (no more than 30%) of vitamin D can be obtained from the diet, since only a few foods naturally contain it (13), therefore generally vitamin D needs are covered by the photochemical conversion of 7-dehydrocholesterol induced by sun ultraviolet B radiation (UVB 290-315 nm). The active form of Vitamin D is produced by 2 hydroxylation steps (14). The first process of hydroxylation takes place in the liver by 25-hydroxylase and forms 25-hydroxyvitamin D3 (25(OH)D3), while the second hydroxylation step that produces the last active metabolite occurs predominantly in the kidney by 1α-hydroxylase. The serum levels of 25(OH)D3 is a good indicator of vitamin D deficiency, since it has a slower clearance than 1,25 (OH)2 D3 (14, 15).

To produce sufficient levels of vitamin D in a person with fair skin, you need to expose 15% of the body

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surface, hands, face and arms or equivalent area of 10 to 15 minutes, 4 to 6 times a week, but it depends on precursor activity of 7-dehydrocholesterol in the skin. Which varies depending on age, ethnicity, season/UV availability, skin colour and use of sunscreen (SPF 12 on factor prevents the generation of vitamin D) (14, 16–18).

Vitamin D deficiency it's a global public health problem ranging between 30-90% of people from different populations (19–22). In Chile a high prevalence of VitD deficiency in postmenopausal women has been described (47.5-60%) (26 ,27). Older people are at higher risk of poor vitamin D status, because they have a decreased ability of the skin to produce cholecalciferol, resulting in a fourfold less production after exposing the skin to UVB radiation worsened by the fact that the elderly tend to be out in the sun less and therefore have reduced sun exposure. Further, the concentration of 7-dehydrocholesterol in the skin of the elderly is 50% less that of young people (23, 24). Also, less renal conversion to its active form, age-associated (19, 25). These conditions could predict that older people present low serum 25(OH)D levels, and therefore they may have an increased risk of metabolic abnormalities that have been previously associated with poor Vitamin D status.

The Objective of this study is to examine the frequency, distribution and metabolic disorders associated with vitamin D deficiency/insufficiency in community-living Chilean older people.

Subjects and Methods

This was a cross-sectional study in 1186 community dwelling subjects 60-98 years old (68% women) residing in Santiago Chile (latitude 33º24'S). The data correspond to the 2008-2011 wave of the "Active Life Expectancy, Aging and Disability Related to Obesity Study" (ALEXANDROS) already described (28, 29). Briefly ALEXANDROS is a longitudinal study of 3 cohorts of community dwelling older adults aimed to explore the trajectories of disability associated with obesity in Chilean older individuals from different socio-economic and demographic backgrounds. a) The SABE cohort (30) formed by 1173 people born before 1940 living in Santiago b) the ALEXANDROS cohort comprising 950 people born between 1940 and 1948, randomly selected from Primary Health Care Centres (PHCC) registries and c) the ISAPRES cohort of 266 people of high socioeconomic level (SEL) born before 1948 randomly selected from private health insurance system registries (ISAPRES) (28). No exclusion criteria were considered.

For the aims of this research, between 2008 and 2011 the available subjects were invited to attend an appointment at the Institute of Nutrition and Food Technology (INTA) for an evaluation. After signing an informed consent approved by the Ethics committee of INTA, all the subjects underwent face-to-face interviews including socio-demographic characteristics, history of chronic diseases, self-reported functional limitations, anthropometric and blood pressure measurements. Height was measured in centimetres recorded to the nearest 0.5 cm by using a Harpenden Pocket Stadiometer (Holtain Ltd., Crosswell, UK) with the subject standing barefoot with heels together and head in the Frankfort horizontal plane. Weight was assessed with a SECA platform scale (Madison, WI, USA) graduated to the nearest 0.1 kg with the subject standing on the platform barefoot and lightly clothed. Waist circumference was assessed to the nearest 0.1 cm. with a flexible steel tape at the upper border of the iliac crest with the subject standing up. Body mass index (BMI) was calculated to classify individuals as normal, overweight, obese or underweight according to the WHO standards (31). Blood pressure was measured using an air sphygmomanometer. The measurement was carried out after 10 minutes of chair rest and recorded twice at an interval of 5 minutes. We used the average of both measurements to determine blood pressure.

A 12 hours fasting blood sample (10 mL) was obtained for glucose, insulin, total cholesterol and HDL cholesterol, Triglycerides, Ultra Sensitive C-Reactive Protein (US-CRP) and 25-hydroxyvitamin D (25(OH)D) determinations. Blood samples were collect along the year except in February.

Diabetes was defined as ≥ 126 mg/dl or use of anti-diabetic agents (32); Fasting glucose intolerance (FGI) was defined as glucose ≥100 mg/dL (32) and insulin resistance as HOMA-IR ≥ 2.6 (33). Metabolic syndrome was identified using ATP III criteria (32). VitD deficiency was defined as a serum 25(OH)D concentration <50 nmol/L, VitD insufficiency as 50-74 nmol/L and sufficient as ≥ 75 nmol/L(34,35). Obesity was defined according WHO criteria (BMI ≥ 30 kg/m2).

Laboratory analyses

Plasma samples were obtained in the morning and frozen at -80 ºC. Plasma levels of 25(OH)D were determined by radioimmunoassay (DiaSorin Stillwater, Minnesota 55082-0285, USA) with quality control materials provided by the manufacturer. The detection limits for 25(OH)D was 6 nmol/l, the intra-assay CV was 10.8% and the inter-assay CV was 9.4%. Insulin was determined by RIA, DPC, INC, The Los Angeles, CA. KIT Coat-a-Count, the intra-assay CV was 5.2% and the inter-assay CV was 7.3. Plasma US-CRP levels were determined using Immunoturbideimetria Method by the Kit: Latex High sensitivity CRP Turbidimetric (Química Clínica Aplicada SA., QCA, CN-Apartado 20- E43870 Amposta/España). Serum glucose, triglycerides, total cholesterol and HDL cholesterol were measured by enzymatic colorimetric assay. All of the intra-and inter-assay coefficients of variation were <10%.

Statistical analyses

Descriptive characteristics for subjects are expressed as means ± standard deviations and 95% CI for continuous variables and frequency (95% CI) for categorical variables. Comparisons of anthropometric and metabolic characteristics were made using t-test or rank-sum test between men and women. Comparisons of variables between groups with different vitamin D statuses were made using Kruskal-Wallis test for continuous variables when not normally distributed or Chi2 for categorical variables. Trend test for across ordered groups (p-trend) were used for continuous and categorical variables. Logistic regression analysis was used to estimate the association of VitD with metabolic disorders adjusting by age, sex, waist circumference and season. We grouped the individuals with samples from the sunniest months of the year in the city (October to March) defining it as summer season.

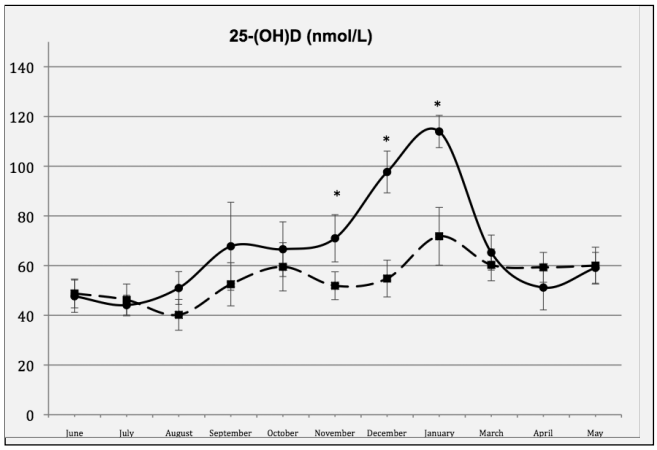
All statistical analyses were performed with STATA software version 12.1 (StataCorp. 2008. Stata Statistical Software: Release 10.1. College Station, TX: StataCorp LP).

Results

Between 2008 and 2011 we studied 1186 subjects, mean age 70.5y ± 6.4, 68% women, 32% men, and mean age 70.4y ± 6.3. The characteristics of the sample are described in table 1. A high prevalence of obesity (37.6%) and abdominal obesity (63.0%), both of which were higher in women (p<0.001) was observed. The prevalence of diabetes was 20.8% and glucose intolerance 44.8%, higher in men than in women (50.3% vs 42.8% p=0.018).

Mean concentration of 25(OH)D was 63.2 ± 33.1 nmol/L in the total population, lower in women (62.0 ± 33.2) than in men (66.0 ± 33.0) p=0.048 and lower in people ≥70 years than in the 60-69y group (55.8 ± 26.6 nmol/L, p<0.001). A high proportion of the sample had levels <75 nmol/L of 25(OH)D (71.4%). The frequency of subjects with plasma concentrations <50 nmol/L was 38.1%, being more common in women than in men (40.5% vs 34.1%, p = 0.045).

Figure 1
25(OH)D for each month of the year starting in June by age



Values are means ± 95% CI, the solid line represents the subjects <70 years (n = 599) and the dotted line to subjects> 70 years (n = 587). * Kruskal-Wallis test p<0.05

Table 1
Characteristics of the sample by gender

	Total n=1186 100%	Women n=807 68%	Men n=369 32%	p value
Waist circumference, cm	94.5 ± 12.1 (93.8-95.2)	92.7 ± 12.4 (92.0-93.6)	98.2 ± 11.0 (97.0-99.3)	<0.001
Waist circumference, ≥102/88 cm	52.6 (49.7-55.5)	63.0 (59.3-66.1)	31.0 (26.3-36.0)	<0.001
BMI, ≥ 30 kg/m2	34.0 (31.2-36.8)	37.6 (34.1-41.0)	26.3 (21.9-31.2)	<0.001
Diabetes Mellitus	20.8 (18.4-23.2)	20.1 (17.4-23.0)	23.0 (18.8-27.7)	0.245
Glucose intolerance	44.8 (42.0-47.7)	42.8 (39.4-46.3)	50.3 (45.0-55.9)	0.018
Metabolic Syndrome	54.2 (51.4-57.1)	57.0 (53.4-60.4)	49.5 (44.2-54.6)	0.016
Hypertension	57.5 (54.5-60.4)	54.2 (50.6-57.8)	64.5 (59.3-69.5)	0.002
Fasting Insulin, uUI/ml	6.4 ± 5.8 (6.0-6.7)	6.5 ± 5.9 (6.1-6.9)	6.1 ± 5.4 (5.5-6.7)	0.207
US-CRP, mg/L	3.0 ± 3.4 (2.9-3.3)	3.3 ± 3.9 (3.0-3.5)	2.7 ± 3.3 (2.3-3.0)	0.006
Fasting Glucose, mg/dl	105.3 ± 31.1 (103.5-107.0)	104.3 ± 30.0 (102.3-106.4)	107.3 ± 33.4 (104.0-111.0)	0.135
Serum total cholesterol, mg/dl	195.6 ± 41.1 (193.3-197.9)	199.5 ± 40.4 (196.7-202.3)	187.0 ± 41.3 (182.8-191.2)	<0.001
Serum HDL cholesterol, mg/dl	38.1 ± 11.4 (37.5-38.8)	39.7 ± 11.7 (38.9-40.5)	34.7 ± 10.0 (33.7-35.7)	<0.001
Serum TG, mg/dl	143.6 ± 78.5 (139.1-148.1)	142.2 ± 72.0 (137.2-147.1)	146.9 ± 91.1 (137.6-156.3)	0.329
Diastolic blood pressure, mm Hg	76.1 ± 11.6 (75.4-76.8)	74.2 ± 11.4 (73.4-75.0)	80.4 ± 10.9 (79.3-81.6)	<0.001
Systolic blood pressure, mm Hg	134.2 ± 19.4 (133.0-135.3)	132.6 ± 19.5 (131.2± 134.0)	137.8 ± 19.0 (135.7- 139.8)	<0.001
25-(OH) D, nmol/L	63.2 ± 33.1 (61.3-65.3)	62.0 ± 33.2 (59.7-64.2)	66.0 ± 33.0 (62.7-69.4)	0.048
25-(OH) D < 50, nmol/L	39.7 (37.0-42.5)	40.8 (37.4-44.3)	36.5 (31.6-41.5)	0.045
25-(OH) D 50-74, nmol/L	31.5 (28.8-34.1)	32.0 (28.8-35.2)	30.3 (25.6-35.0)	0.847
25-(OH) D ≥ 75, nmol/L	28.6 (26.0-31.2)	27.0 (23.9-30.0)	33.0 (28.2 -37.8)	0.020

Data are mean ± SD (95%CI) or % (95%CI);P value = ttest.

Table 2
Characteristics of study participants according plasma 25(OH)D (nmol/L) categories

	25 (OH)D, nmol/L			
	<50	50 to 74	≥ 75	p-trend
N	470	374	342	
Age, y*	72.0 ± 7.0 (71.4-72.7)	70.8 ± 6.2 (70.2-71.5)	68.0 ± 4.9 (67.4-68.5)	<0.001
Diabetes mellitus % (95%CI)	19.7 (16.2-23.6)	23.2 (19.0-27.8)	19.7 (15.6-24.3)	0.922
Glucose intolerance % (95%CI)	46.7 (42.1-51.3)	44.5 ,(39.3-49.7)	42.9 (37.6-48.3)	0.281
BMI, kg/m2* mean ± SD (95%CI)	29.2 ± 5.2 (28.7-29.7)	28.7 ± 4.8 (28.2-29.2)	28.3 ± 4.7 (27.8-28.8)	0.001
Waist circumference, cm* mean ± SD (95%CI)	95.6 ± 12.4 (94.5-96.7)	93.6 ± 12.2 (92.4-94.8)	93.7 ± 11.9 (92.4-95.0)	0.020
Systolic blood pressure, mm Hg* mean ± SD (95%CI)	136.8 ± 19.6 (135.0-138.7)	133.8 ± 19.4 (131.7-135.9)	131.0 ± 18.8 (128.9-133.0)	<0.001
Diastolic blood pressure, mm Hg mean ± SD (95%CI)	76.9 ± 12.3 (75.7-78.0)	76.0 ± 11.3 (74.8-77.2)	75.3 ± 11.2 (74.1-76.5)	0.066
Fasting Glucose, mg/dl mean ± SD (95%CI)	106.0 ± 29.2 (103.2-108.8)	107.7 ±32.2 (104.3-111.2)	104.3 ± 33.5 (100.7-107.9)	0.067
Fasting Insulin, uUI/ml* mean ± SD (95%CI)	7.1 ± 6.3 (6.5-7.7)	6.0 ± 5.4 (5.4-6.6)	5.9 ± 5.3 (5.4-6.5)	0.011
HOMA-IR*	2.0 ± 2.1 (1.7-2.1)	1.7 ± 2.0 (1.5-1.9)	1.6 ± 2.0 (1.4-1.8)	0.011
US-CRP, mg/l mean ± SD (95%CI)	3.2 ± 3.5 (2.8-3.5)	3.1 ± 3.6 (2.7-3.5)	3.0 ± 3.1 (2.7-3.3)	0.942
Metabolic Syndrome % (95%CI)**	61.7 (56.9-66.3)	53.2 (47.7-58.5)	52.7 (47.1-58.1)	0.048

Data are mean ± SD (95%CI) or % (95%CI); * Kruskal-Wallis test p<0.05; ** Pearson chi2 p<0.05; p-trend: test across ordered groups

The concentrations of 25(OH)D were different depending on the season of the year highest in the samples obtained in January (mean = 106 ± 36.3 nmol/L) peak summer month in Chile. On the other side the lowest values were obtained in July (mean 45.8 ± 19.0 nmol/L) peak winter month (Figure 1). The prevalence of deficiency in last spring, summer and beginning fall months was much lower than the prevalence in samples obtained since April to September (28.7% vs 50.3%, p<0.001). About a half of subjects were enrolled in fall and winter months (n=599) and the other half in spring and summer months (n=587).

Serum US-CRP was 3.3 ± 3.9 mg/L, higher (p = 0.006) in women (3.3 ± 3.9) than in men (2.7 ± 3.3). Women have higher frequency of metabolic syndrome than men (57.0% vs 49.5%, p = 0.016).

The characteristics of the sample by categories of VitD status are presented in table 2. The people with Vit D deficit were more aged, had higher BMI, waist circumference, systolic blood pressure, fasting insulin, HOMA-IR and metabolic syndrome than people with insufficient or normal status of Vit D levels. Significant p trend across groups was observed for the same variables.

A logistic regression analysis was performed to assess the association of vitamin D deficiency on insulin resistance (defined as HOMA-IR > 2.6) adjusted by gender, age, waist circumference and season of the year (Table 3). Significant association of 25(OH)D <50 nmol/L with IR (OR=3.12, p<0.001) adjusted by waist circumference ≥102/88 (OR=5.88, p<0.001) was observed. A significant interaction of VitD<50 nmol/L with waist circumference was observed (p<0.010). Thus increasing the association (OR =7.04; 95%CI 3.99- 12.45) for the subjects with VitD<50 and waist circumference≥102/88cm.

Table 3
Logistic Regression for insulin resistance according vitamin D, age, season, waist circumference and sex

Insulin resistance	OR (95%CI)	p value
VitD <50 nmol/L	3.12 (1.66-5.86)	<0.001
Age ≥ 70 years	0.93 (0.67-1.29)	0.642
Summer season	1.15 (0.83-1.60)	0.388
Waist circumference ≥102/88	5.88 (3.39-10.18)	<0.001
Female	0.72 (0.50-1.05)	0.094
VitD <50* Waist circumference ≥102/88	0.38 (0.18-0.80)	0.010

Insulin resistance was defined HOMA-IR > 2.6.

Discussion

This study shows that Chileans older people living in the community have a very high frequency of vitamin D deficiency (40%); over 50% of the subjects had vitamin D insufficiency, and the proportion increased with older age and in women. the Two previous studies in Chilean in postmenopausal women, have shown similar frequencies (47.5 and 60%) of VitD deficiency (26, 27). Although high, our study shows lower frequency of vitamin D deficiency than a similar study done in Argentina (36) founding a prevalence of 64% in older people living at home in de mid region of the country

with same average latitude than Santiago, Chile (33ºS).

We found also significant association with obesity especially abdominal fat. These results are similar to several studies that have shown that deficiency of plasma levels of 25(OH) D is associated with obesity, including increased BMI, percentage fat mass and waist circumference (37, 38). Recently a large study of Jorde et al. 2010 done in 10,229 subjects, showed a negative association between 25(OH) D levels and BMI (39). Although mechanisms are not totally elucidated considering the high lipo-solubility of VitD, increased adiposity may result in diminished bioavailability due to sequestration of VitD in adipose tissue (40).

Furthermore, plasma levels below 50 nmol/L were associated with Metabolic Syndrome; this result agrees with that shown by X. Yin et al. 2012 where in a middle-aged population (30-60y) there were high levels of deficiency and insufficiency of vitamin D associated with metabolic syndrome (12). We have also found a negative association with insulin resistance. The association persist after accounting for potential confounders and the interaction between vit D and waist circumference. Several studies have associated low levels of 25(OH) D with the development of insulin resistance in different populations (41), even more, in some clinical studies have shown that high levels of this vitamin is a good predictor of good performance of beta cells and better glycaemia in subjects at high risk for type 2 diabetes (PROMISE cohort) (42). It has been observed in vitro and animal studies that vitamin D may play a role in glucose homeostasis through its effect on the synthesis, secretion and insulin sensitivity (6, 7). It has been proposed that the beneficial effect of vitamin D in insulin sensitivity would increase through the insulin receptor mRNA; Maestro et al. 2002 treated human cells promonocytic U-937 with 108M 1,25(OH)2D3 and saw that this increased insulin receptor mRNA would be mediated possibly through the up-regulation of the activity of phosphatidylinositol 3-kinase. U-937 cells have many characteristics of circulating monocytes, naturally have many hormone receptors including VitD receptor (VDR) and insulin receptor (IR), therefore have been used in regulation studies of IR expression and insulin action mediated by 1,25 (OH)2D3. (43). Vitamin D deficiency has different roles in the development of insulin resistance. Gene polymorphisms in VDR, Vitamin D Binding Protein (DBP) or vitamin D 1alpha-hydroxylase (CYP1alpha) may disrupt vitamin D production, transport and action (44, 45). Deficiency of Vitamin D activate the innate and adaptive immunity, enhancing dendritic cell maturation and differentiation of macrophages to increase the release of cytokines (IL-12, IL-2, INF-γ and TNF-α), which can cause β-cell destruction leading to insulin resistance (46). Vitamin D plays an immunoregulatory function inhibiting the release of pro-inflammatory cytokines such as TNF-α, regulates the activity of NF-κB, and suppresses the expression of TLR2 and TLR4 protein and mRNA in human monocytes, resulting in a reduction in cytokine release. Therefore VitD plays an important role reducing insulin resistance and the risk of diabetes and metabolic syndrome by reducing the inflammatory response (44, 47). However, further studies are needed to elucidate the pathways achieve action of vitamin D metabolites in the actions of insulin on glucose metabolism.

Moreover, we found no association with type 2 diabetes, although with insulin resistance and metabolic syndrome. This could be explained considering that in older adults, the insulin resistance is less gravitating; the main pathogenic factor of type 2 diabetes is the lack of insulin secretion.

Among the limitations the cross-sectional study design does not allow us to discard the association found is caused by excess of adiposity in people with metabolic disorders. Measurements for VitD conducted all along the year even when the results were adjusted for seasonality and the number of people who were taken in winter is similar to summer. We didn't measure PTH, although two previous studies done in Argentina and Brazil (Oliveri 2004, Unger 2010) (36, 48) found significant but relatively weak correlation between Vit D and PTH (R=-0.24 –0.20 respectively).

The strength of this study is that it was able to recruit a large number of subjects representing different socioeconomic and demographic stratus of Santiago de Chile capital city of the country were 39.2% of Chilean older adults live. To our knowledge this is the first study in Chile investigating the association of metabolic disorders with vit D Deficiency.

Considering the important problems associated to VitD deficiency/insufficiency, the results of the study rise the challenge for the generation of integral strategies facing this problem by the country.

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