European Journal of Clinical Nutrition (2013) **67,** 680–682

www.nature.com/ejcn

SHORT COMMUNICATION

Hypovitaminosis D and incidence of obesity: a prospective study

I González-Molero[1,2], G Rojo-Martínez[1,2], S Morcillo[1,2], C Gutierrez[1,2], E Rubio[1,2], V Pérez-Valero[3], I Esteva[1,2], MS Ruiz de Adana[1,2], MC Almaraz[1,2], N Colomo[1,2], G Olveira[1,2] and F Soriguer[1,2]

The aim of this study was to assess the relationship between obesity and vitamin D status cross-sectionally, the relationship between obesity and the incidence of hypovitaminosis D prospectively and inversely the relationship between vitamin D status and incidence of obesity in a population-based cohort study in Spain. At baseline (1996–1998), 1226 subjects were evaluated and follow-up assessments were performed in 2002–2004 and 2005–2007, participants undergoing an interview and clinical examination with an oral glucose tolerance test. At the second visit, 25-hydroxyvitamin D and intact parathyroid hormone concentrations were also measured. Prevalence of obesity at the three visits was 28.1, 36.2 and 39.5%, respectively. The prevalence of vitamin D deficiency (25-hydroxyvitamin D $\leqslant$20 ng/ml ($\leqslant$50 nmol/l)) was 34.7%. Neither obesity at baseline (OR = 0.98, 95% CI: 0.69-1.40, $P = 0.93$) nor the development of obesity between baseline and the second evaluation (OR = 0.80, 95% CI: 0.48–1.33, $P = 0.39$) were significantly associated with vitamin D status. In subjects who were non-obese (BMI <30 kg/m^2) at the second evaluation, 25-hydroxyvitamin D values $\leqslant$17 ng/ml ($\leqslant$42.5 nmol/l) were significantly associated with an increased risk of developing obesity in the next 4 years (OR = 2.35, 95% CI: 1.03–5.4, $P = 0.040$ after diverse adjustments). We conclude that vitamin D deficiency is associated with an increased risk of developing obesity.

European Journal of Clinical Nutrition (2013) **67,** 680–682; doi:10.1038/ejcn.2013.48; published online 20 February 2013

Keywords: vitamin D; obesity; 25-hydroxyvitamin D; weight; prospective study

INTRODUCTION

A complex relationship has been described between obesity and vitamin D concentrations. Previous cross-sectional studies suggest an inverse relation between body mass index (BMI) and fat mass, with low concentrations of 25-hydroxyvitamin D and high concentrations of intact parathyroid hormone (iPTH).[1]

Adipocytes can express the vitamin D receptor and can secrete the enzyme 1-α-hydroxylase; thus, local activation of vitamin D may contribute to, and be regulated by adipose tissue function.[2] However, whether obesity is responsible for low 25-hydroxyvitamin D concentrations, or whether hypovitaminosis D can lead to obesity, or even whether there are regulatory interactions between obesity and vitamin D activity remains unclear.

Accordingly, the aim of this study was to assess the relationship between obesity and vitamin D status within the Pizarra study, a 12-year, prospective, population-based study undertaken in southern Spain.

MATERIALS AND METHODS

The Pizarra study is a prospective, population-based study undertaken in Pizarra, Málaga, in southern Spain. The baseline study was undertaken during 1996–1998, with the inclusion of 1226 subjects. Of the initial cohort, 988 subjects were re-evaluated in 2002–2004, and 961 subjects were re-evaluated later in 2005–2007. At both the baseline and the follow-up visits, all the participants underwent an interview and a standardized clinical examination. Measurements were made of weight, height, waist and hip circumferences. The BMI was calculated as weight in kg divided by height in m^2. A BMI $\geqslant$30 kg/m^2 was considered as obesity. The same methodology was used for the baseline and the follow-up studies.

A fasting blood sample was drawn at baseline and at the follow-up visits in all subjects. Serum was stored at $-80\,^{\circ}$C for later analysis. Measurements of 25-hydroxyvitamin D and iPTH concentrations were made at the second visit. An oral glucose tolerance test was performed in those subjects without known diabetes at each visit. Values of 25-hydroxyvitamin D $\leqslant$20 ng/ml were considered to represent vitamin D deficiency according to Endocrine Society recommendations. Diabetes was diagnosed and classified according to the 2011 American Diabetes Association criteria.

The protocol was approved by the Ethics and Clinical Research Committee of Carlos Haya Hospital, Malaga. All the participants provided written informed consent.

Glucose (mg/dl) was measured by hexoquinase-glucose-6-phosphate dehydrogenase (Dimension Vista System, Siemens, Erlangen, Germany). 25-hydroxyvitamin D (ng/ml) levels were measured by electro-chemiluminescence (ECLIA immunoassay, Modular Analytics E170, Roche, Roche Diagnostics GmbH, Mannheim, Germany) (sensitivity 4–100 ng/ml, own intraassay coefficient of variation (CV): 7.30%, interassay CV: 13,02%) (This assay does not detect D2 metabolites well and has less precision than others).[3] Intact parathyroid hormone (pg/ml) was measured by electrochemiluminescence (ECLIA immunoassay, Modular Analytics E170, Roche), (sensitivity 1.20–5000 pg/ml, CV 7.02%).

Statistical analysis

Continuous variables are presented as the mean and standard deviation or percentiles, and categorical variables as percentages. The normality of the distribution of the continuous variables was determined by the Shapiro–Wilks test. To evaluate the association between obesity and 25-hydroxyvitamin D concentrations, the odds ratio (OR) and 95% confidence intervals (CI) were calculated using a logistic regression model. In all cases, the level of rejection of a null hypothesis was $\alpha = 0.05$.

[1]Servicio de Endocrinología y Nutrición, Hospital Regional Universitario Carlos Haya de Málaga, Málaga, Spain; [2]Ciber de Diabetes y Metabolismo (CIBERDEM), Barcelona, Spain and [3]Laboratorio de Análisis Clínicos. Hospital Regional Carlos Haya de Málaga, Málaga, Spain. Correspondence: Dr I González-Molero, Servicio de Endocrinología y Nutrición, Hospital Regional Universitario Carlos Haya de Málaga, Avenida Dr Gálvez Ginachero s/n, Pabellón C, Hospital Civil, sótano P1, Malaga 29009, Spain.
E-mail:inmagonzalezmolero@hotmail.com
Received 26 September 2012; revised 24 January 2013; accepted 25 January 2013; published online 20 February 2013

Table 1. Clinical and biochemical characteristics of the participants at each visit

	Baseline	*Second visit*	*Third visit*
Age (years): mean ± s.d. and range	40.2 ± 13.3 (18–68)	46.2 ± 13.7 (23–72)	52.1 ± 13.2 (27–77)
Sex (male) (%)	37.1	36.9	38.1
BMI (kg/m^2): mean ± s.d. and range	27.5 ± 4.9 (16.3–46.9)	28.7 ± 5.2 (16.6–51.9)	29.3 ± 5.5 (18–64–49.7)
Obesity (BMI ⩾ 30) (%)	28.1	36.2	39.5
Diabetes (%)	13.4	20.3	17.3
25-hydroxyvitamin D (ng/ml): mean ± s.d. and range		22.8 ± 6.2 (5.4–50.5)	
iPTH levels (pg/ml): mean ± s.d. and range		43.9 ± 17.9 (13.2–96.2)	
25-hydroxyvitamin D < 20 ng/ml (%)		34.7	
25-hydroxyvitamin D < 30 ng/ml (%)		88.9	

Abbreviation: BMI, body mass index.

RESULTS

The clinical and biochemical characteristics of the participants at each visit are shown in Table 1. In cross-sectional study at the second visit, 25-hydroxyvitamin D values were lower in obese subjects (23.3 ± 6.3 vs 21.9 ± 6.2 ng/ml, $P = 0.002$). However, no significant association was found between vitamin D deficiency and obesity after adjustment for sex, age, season, iPTH values and the diagnosis of diabetes (OR = 1.052, 95% CI: 0.76–1.44, $P = 0.75$).

Weight and incidence of vitamin D deficiency

In subjects who were obese at baseline (first evaluation), the prevalence of vitamin D deficiency at the second evaluation was 38.9 vs 32.6% in those who were not obese at baseline. This difference was not significant after adjustment for sex, age, season, iPTH values and the diagnosis of diabetes (Table 2). Neither weight increase during the 6 years of follow-up between baseline and the second visit, nor the development of obesity during this period was significantly associated with the prevalence of vitamin D deficiency at the second evaluation (Table 2).

Vitamin D deficiency and incidence of obesity

Subjects with 25-hydroxyvitamin D values ⩽17 ng/ml at the second evaluation were more likely to be obese at the third evaluation than subjects with 25-hydroxyvitamin values >17 ng/ml at the second evaluation (19 vs 9.5%, $P = 0.03$) (Table 2). After adjusting the model for sex, age, season, iPTH values and the diagnosis of diabetes, the OR for developing obesity between the second and third evaluations in subjects with 25-hydroxyvitamin D values ⩽17 ng/ml was 2.35 (95% CI: 1.03–5.34, $P = 0.04$) (Table 2). The OR of gaining ⩾3.7 kg (75th percentile) between the second and third evaluations in subjects with 25-hydroxyvitamin D values ⩽17 ng/ml was 2.37 (95% CI: 1.23–4.58, $P = 0.01$) (Table 2).

Table 2. Incidence of vitamin D deficiency in second study according to baseline obesity and incidence of obesity in third study according to vitamin D deficiency in second study

Risk of vitamin D deficiency (⩽20 ng/ml) in second study

	95% confidence interval			P-*value*
	OR	*Lower*	*Upper*	
BMI at baseline				
⩾30	0.98	0.69	1.40	0.93
<30	1(RC)			
Weight difference between baseline and second study	0.993	0.961	1.025	0.65
Obesity development between baseline and second study	0.80	0.48	1.33	0.39

Risk of developing obesity between second and third study

	OR	*Lower*	*Upper*	
25-hydroxyvitamin D (ng/ml)				
>17	1(RC)			
⩽17	2.35	1.03	5.34	0.04

Risk of weight increase higher than 3.7 kg (75th percentile[a]) between second and third study

25-hydroxyvitamin D (ng/ml)				
>17	1(RC)			
⩽17	2.37	1.23	4.58	0.01

Abbreviations: BMI: body mass index, RC, reference criterion. Regression logistic model. Model adjusted for age, sex, season, iPTH and the presence of diabetes. First study: 1996–1998, second study: 2002–2004 and third study: 2005–2007. [a]3.7 kg: 75th percentile of the weight gain distribution between the second and third study in non-obese subjects of second study.

DISCUSSION

The results of the present study suggest that lower 25-hydroxyvitamin D values in obese subjects may not have been secondary to obesity, but may in fact precede obesity. Different cross-sectional studies have reported a high prevalence of vitamin D deficiency in obese subjects, as well as significantly lower 25-hydroxyvitamin D values in obese than in non-obese subjects.[1] We found similar results in the initial analysis, but this relationship disappeared after the model was adjusted for sex, age, season, iPTH values and the diagnosis of diabetes (we adjusted for iPTH because 25-hydroxyvitamin D and iPTH were negatively correlated in this study and because iPTH and obesity could have been related. After analysis, iPTH did not correlate with obesity when we adjusted for 25-hydroxyvitamin D concentration; data not shown). Few prospective studies have addressed this issue, mostly with contradictory results. Some studies found that BMI, waist–hip ratio and the percentage of fat mass were associated with later lower vitamin D status.[1,4] On the other hand, an improvement in vitamin D status has been reported after weight loss, either as a result of a hypocaloric diet and exercise or bariatric surgery.[2]

Thus, the relationship between obesity and vitamin D still remains unclear. It may have a multifactorial etiology, involving such factors as inadequate sun exposure, less exercise in obese subjects due to reduced mobility, suboptimal intake of vitamin D, increased storage of vitamin D in adipose tissue, an increased activity of the 24 hydroxylase enzyme in adipose tissue that promotes vitamin D catabolism, or a decreased production of 25-hydroxyvitamin D in the liver due to hepatic steatosis.[2]

The relationship between vitamin D and adipose tissue does not seem to be reduced to a mere storage function, and adipocytokines and inflammatory mediators produced in adipose tissue may have an important role.[4] Whether visceral or subcutaneous fat is more likely to be involved with lower values of vitamin D is not well known.[5] Some authors have noted that after ultraviolet B radiation exposure, obese subjects have a lower increase in vitamin D values than non-obese subjects and even after oral vitamin D supplementation, obese subjects have a lower increase in vitamin D values than non-obese subjects,[6] which highlights the role of subcutaneous fat in vitamin D storage.[6] However, other authors have found that visceral fat is more relevant than BMI in determining vitamin D values, which supports the prominent role of visceral fat and its cytokine and inflammatory mediators production.[4] In this regard, the study of Cheng *et al.*[5] is very interesting because they performed scanner studies to asses subcutaneous and visceral fat volume. Both volumes were associated independently with vitamin D values, but the association was stronger for visceral fat. The relationship between 25-hydroxyvitamin D concentration and visceral fat was maintained for all values of BMI, however the relationship between subcutaneous fat and vitamin D disappeared for subjects with lower BMI.

Recent studies have found that adequate vitamin D status protects against the development of obesity. Ortega *et al.*[7] observed in 60 women that baseline 25-hydroxyvitamin D values predict weight loss after a hypocaloric diet during 2 weeks. A prospective study in children demonstrated that lower values of 25-hydroxyvitamin D were associated with an increase in BMI and waist circumference after 3 years of follow-up.[8] Mai *et al.*[9] evaluated 2165 subjects with a BMI <30 and found that 25-hydroxyvitamin D values $\leqslant 50$ nmol/l were associated with an increased risk of obesity. Shahar *et al.*[10] found a relationship between vitamin D status and weight loss in 126 subjects who were followed up for 2 years. Other data suggesting that vitamin D can modulate the incidence of obesity were reported by Teegarden *et al.*,[11] who observed that higher values of 25-hydroxyvitamin D determine an increased thermogenic effect of food and Chan She Ping-Delfos *et al.*[12] who observed that after oral supplementation of calcium and vitamin D, there was an immediate reduction of food intake, a longer time between meals, and a lower food intake in the next 24 h. As other studies found no positive effect of vitamin D status on weight loss and obesity incidence,[13,14] Earthman *et al.*[2] concluded in a recent review that there is not enough evidence to declare whether vitamin D reduces, increases or does not modify the risk of obesity.

The mechanisms involved in the action of vitamin D on the activity and differentiation of adipose tissue are still largely unknown. One of these pathways could be because 1,25-hydroxyvitamin D may block the differentiation of adipose tissue, suppressing the activity of lipoprotein lipase, aP2, PPAR-γ, C/EBP-α and SREBP-1, although other mechanism can be involved.[2]

CONCLUSION

The discordant results of previous studies could be due to the different designs, since cross-sectional studies do not allow the establishment of a causal relationship, whereas prospective studies could include confounding variables during analysis that can modify the association between the study variables; moreover, different nutritional and weather patterns may not have been taken into account. Nevertheless, certain pathophysiological arguments exist, as discussed above, to suggest that the relationship between vitamin D status and obesity may work both ways. The design and features of the Pizarra study allow the evaluation of vitamin D status and obesity in both directions in the same population. Our results suggest that vitamin D status may determine the incidence of obesity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was undertaken with finance from the Fondo de Investigacion Sanitaria (PIO51307) and Junta de Andalucía (PIO258/2007, P06-CTS-01684) CIBER de Diabetes y Enfermedades metabólicas is an ISCII project.

REFERENCES

1 Jorde R, Sneve M, Emaus N, Figenschau Y, Grimmes G. Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: the Tromsøstudy. *Eur J Nutr* 2010; **49**: 401–407.
2 Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating25-hydroxyvitamin D concentrations: considerations and implications. *Int J Obes* 2011; **36**: 387–396.
3 Wagner D, Hanwell HE, Vieth R. An evaluation of automated methods for measurement of serum 25-hydroxyvitamin D. *Clin Biochem* 2009; **42**: 1549–1556.
4 Ding C, Parameswaran V, Blizzard L, Burgess J, Jones G. Not a simple fat-soluble vitamin: changes in serum25-(OH)D levels are predicted by adiposity and adipocytokines in older adults. *J Intern Med* 2010; **268**: 501–510.
5 Cheng S, Nassaro J, Fox C, Larson M, Keyes M, McCabe E *et al.* Adiposity, cardiometabolic risk and vitamin D status: the Framingham Heart Study. *Diabetes* 2010; **59**: 242–248.
6 Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; **72**: 690–693.
7 Ortega RM, Aparicio A, Rodrıiguez-Rodrıiguez E, Bermejo LM, Perea JM, Lopez-Sobaler AM *et al.* Preliminary data about the influence of vitamin D status on the loss of body fat in young overweight/obese women following two types of hypocaloric diet. *Br J Nutr* 2008; **100**: 269–272.
8 Gilbert-Diamond D, Baylin A, Mora-Plazas M, Marin C, Arsenault JE, Hughes MD *et al.* Vitamin D deficiency and anthropometric indicators of adiposity in school-age children: a prospective study. *Am J Clin Nutr* 2010; **92**: 1446–1451.
9 Mai XM, Chen Y, Camargo CA, Langhammer A. Cross-sectional and prospective cohort study of serum 25-hydroxyvitamin D level and obesity in adults. The HUNT Study. *Am J Epidemiol* 2012; **175**: 1029–1036.
10 Shahar DR, Schwarzfuchs D, Fraser D, Vardi H, Thiery J, Fiedler GM *et al.* Dairy calcium intake, serum vitamin D, and successful weight loss. *Am J Clin Nutr* 2010; **92**: 1017–1023.
11 Teegarden D, White KM, Lyle RM, Zemel MB, Van Loan MD, Matkovic V *et al.* Calcium and dairy product modulation of lipid utilization and energy expenditure. *Obesity (Silver Spring)* 2008; **16**: 1566–1572.
12 Chan She Ping-Delfos W, Soares M. Diet induced thermogenesis, fat oxidation and food intake following sequential meals: Influence of calcium and vitamin D. *Clin Nutr* 2011; **30**: 376–383.
13 Young KA, Engelman CD, Langefeld CD, Hairston KG, Haffner SM, Bryer-Ash M *et al.* Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. *J Clin Endocrinol Metab* 2009; **94**: 3306–3313.
14 Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K *et al.* Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr* 2009; **89**: 1321–1327.