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Body mass index represents a good predictor of vitamin D status in women independently from age

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SUMMARY

Background & aims: Vitamin D is a pleiotropic hormone targeting several tissues and is involved in basic homeostatic processes, including bone mineralization, immune response and muscle strength. Although hypovitaminosis D is common in Europe and North America, representing a risk factor for several chronic diseases, the contribution of factors other than sun exposure is largely underestimated.

Methods: In our study, we retrospectively collected data from medical records of women with age between 19 and 80 screened in Central Italy (42°N) for increased risk of metabolic syndrome. Vitamin D status was evaluated by serum 25-hydroxyvitamin D (25(OH)D) measurement and the association among vitamin D status and anthropometric and clinic variables was tested by multivariate logistic analysis.

Results: More than 80% of women presented serum 25(OH)D concentration lower than 30 ng/mL (75 nM), with the majority of values falling between 10 and 20 ng/mL. 25(OH)D concentration was dependent on season, with the highest 25(OH)D mean value measured in September and the lowest mean value in March. Among different clinical characteristics, body mass index (BMI) demonstrated the highest significant inverse correlation with serum 25(OH)D values, independently from season and age. Serum 25(OH)D values demonstrated a seasonal-directed sinusoidal trend and they raised during spring/summer in a similar manner in both obese and non-obese women. However, the obese group had lower mean values of vitamin D respect to overweight and to normal weight groups in both winter and summer, reaching frequently the status of vitamin D deficiency (<10 ng/mL).

Conclusions: In conclusion, at our latitude, seasonal UV irradiance availability determines an obligate sinusoidal trend in vitamin D status. However, body mass is able to reduce proportionally circulating vitamin D over calendar months determining vitamin D deficiency. These results suggest taking in particular account BMI in clinical management of vitamin D status in overweight and obese women.

1. Introduction

Hypovitaminosis D represents a worldwide public health concern [1]. Insufficient levels of vitamin D are not a new condition in human history, in fact several records indicate that hypovitaminosis D had periodically in the past epidemic manifestations with relevant clinic impact [2]. This phenomenon is firmly dependent on the peculiar metabolism of vitamin D that must be photosynthesized in the skin by a restricted ultraviolet spectrum of the sun irradiation. Alternatively, sufficient amounts of vitamin D are difficult to reach by diet only. Data from numerous studies indicate

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that sun exposure is the main source of vitamin D in humans and it is now clear that insufficient levels of vitamin D are endemic in people who do not expose their skin to sun for a sufficient time when UV irradiation is adequate, also in persons who follow an exclusion diet [3–5].

Classic signs of hypovitaminosis D are associated with bone disease, rickets in child and osteomalacia in adults, and thus the high risk categories more frequently under investigation for vitamin D status are young subjects and the elderly, mainly women. In particular, several epidemiologic studies have focused on hypovitaminosis D in postmenopausal women, a population frequently affected by osteoporosis and by aberrant calcium homeostasis [6]. Although the effectiveness of vitamin D supplementation in preventing or treating osteoporosis is debated [7], in the last decades new non-skeletal roles of vitamin D have been proposed. These are collectively considered subclinical effects of hypovitaminosis D, and have been frequently associated with muscular, metabolic and cardiovascular diseases [8–10]. Although the scientific community is awaiting more solid evidence for non-skeletal effects of vitamin D, there is a general consensus in considering vitamin D status as a good predictor of wellbeing [11].

High latitude, winter season and sun avoidance are the main risk factors contributing to maintain year-long low levels of vitamin D. More recent studies have suggested that further risk factors could be represented by age and fat mass. In the elderly, the complex metabolism of vitamin D could be compromised in different checkpoints, from a decline in the ability to synthesize 1,25(OH)D to an increase in its catabolism [12]. In addition, it was reported that in aging skin there is a decline in the cutaneous levels of the vitamin D precursor, 7-dehydrocholesterol [13]. At the same time, there is not a wide agreement in retaining these changes physiologically relevant [14]. On the contrary, wider consensus is reserved to the detrimental role of body fat on circulating vitamin D. Epidemiological studies have frequently shown increasing hypovitaminosis D with increasing body mass index (BMI) [15,16]. However, besides the molecular cause of this inverse correlation, the impact of BMI in lowering 25(OH)D respect with other factors is poorly understood [17].

The aim of our study was to evaluate the seasonal variation of serum 25(OH)D concentration in a population of non-hospitalized women at increased risk for metabolic disease, focusing on other potential determinants of this variation. The main variables considered were age and BMI, and their effects on vitamin D status were evaluated in absence of vitamin D supplementation.

2. Subjects and methods

2.1. Study design and population

We performed a retrospective cohort study using record data from 198 women resident in Abruzzo region (central Italy, Lat. 42°N) and screened in the OU of Metabolic Disease and Nutrition Pathophysiology, Giulianova Hospital (Italy) from 2015 to 2017. The study was conducted in collaboration with the University of L'Aquila and was approved by the local Ethical Committee (n. 28478 27/09/2017). Patients considered in our study had as main feature one of the following conditions: overweight, obesity, hyperlipidemia, high blood pressure, type II diabetes. The Body Mass Index (BMI) was calculated for each subject by dividing the body weight (expressed in kilograms) by the height (expressed in meters) squared. As inclusion criteria we considered: normal weight women with BMI from 18.5 to 25, overweight women with BMI from 26 to 29.9 and obese women with BMI >30; age from 19 to 80; subjects with skin types II and III following the Fitzpatrick Skin Type Classification Scale (these skin types were the most prevalent ones in central Italy). Exclusion criteria encompassed skin diseases, renal failure, thyroid or liver dysfunction, autoimmune diseases, previous vitamin D supplementation. In detail, we collected data about age, nationality, height, weight, blood pressure, physical activity, smoke habit, alcohol consumption, total cholesterol, HDL, triglycerides, fasting glycemia and insulinemia (data are summarized in Table 1). Serum 25(OH)D was evaluated by a direct competitive immunoluminometric assay using coated magnetic microparticles according to the manufacturer guide (LIAISON 25 OH Vitamin D total, Diasorin, Saluggia, Italy).

2.2. Statistical analysis

Descriptive data were presented as mean ± standard deviation (SD) and median with 95% confidence interval. Comparison between two means was performed by Student's t test, and comparison of three BMI categories (normal weight, overweight and obesity) was performed by analysis of covariance. Partial regression model was used as method to describe the relationship between two variables, considering covariables. A linear regression model was generally adopted, except for the correlation between all months and vitamin D for which an equation for sine curve was elaborated ($y = a+b \times \sin((2\pi x/12)+c)$. Box and whisker plot was used as preferred graph for comparing groups. The distribution of mean 25(OH)D levels was plotted by calendar month. All analyses and graphs were realized by using the MedCalc statistical software version 13.0.6 (MedCalc Software bvba, Ostend, Belgium). $P < 0.05$ was considered the acceptable level for statistical significance.

3. Results

In our study, we analyzed vitamin D status in 198 women evaluated in OU of Metabolic Disease and Nutrition Pathophysiology, Giulianova Hospital (central Italy). We selected subjects who sought medical assistance for signs and symptoms associated to increased risk for metabolic syndrome, such as dyslipidemia, hypertension, diabetes and obesity. Table 1 summarizes anthropometric and clinical characteristics of study population, grouping women according to menopausal status. The menopausal status did not result to be a significant discriminant variable for the majority of analyzed characteristics, including serum vitamin 25(OH)D concentration, BMI and waist circumference. Beside age, a significant difference in the mean values was showed only for height, fasting glucose and systolic blood pressure. The majority of subjects (>70%) had 25(OH)D values lower than 30 ng/mL (vitamin D sufficient limit) with a mean value of 20.2 ng/mL (Fig. 1A). When considering all subjects, serum 25(OH)D concentration demonstrated a significant difference between the mean value measured in central months of the year (from April to September, “high D-season”) respect to the mean value measured in other months (“low D-season”, 22.8 ± 10.8 vs 17.7 ± 9.9, $P < 0.01$) (Fig. 1B, Supp. Table 1). When comparing high and low D-season we did not observe significant differences in age, BMI, or waist circumference measure (Supp. Table 1). The partial correlation analysis demonstrated a robustly significant inverse association between 25(OH)D concentration and BMI, but not between 25(OH)D and other potential correlates, such as age and calendar months (Supp. Table 2). Correlation between BMI and 25(OH)D was modeled with the regression equations shown in Fig. 2. The model indicated a reduction of 0.5 ng/mL 25(OH)D per 1 unit increase in BMI, and the correlation was statistically significant both in high and low D-seasons ($P < 0.01$). The same trend was calculated for the association between waist measure and vitamin D with a significant reduction of 0.15 ng/mL 25(OH)D per 1 cm increase in waist measure (data not shown). In order to evaluate the influence of BMI in

Table 1
Anthropometric and clinical variables of study population, stratified in two subgroups according to menopause status. For each variable mean value and standard deviation (SD), and median and 95% confidence interval (95% CI) were calculated.

		Total (N = 198)	Premenopause group (N = 94)	Postmenopause group (N = 104)	P*
Age (years)	Mean ± SD	50.7 ± 14.9	40.0 ± 12.3	60.4 ± 9.4	<0.01
	Median (95% CI)	52.0 (49.0:54.0)	42.0 (39.0:45.0)	59.0 (56.0 ± 62.0)	
Height (m)	Mean ± SD	1.59 ± 0.07	1.61 ± 0.07	1.56 ± 0.07	<0.01
	Median (95% CI)	1.59 (1.57:1.60)	1.60 (1.59:1.61)	1.56 (1.54:1.58)	
Weight (kg)	Mean ± SD	78.0 ± 20.9	77.8 ± 23.8	78.2 ± 17.9	0.89
	Median (95% CI)	75.0 (71.9:78.0)	72.1 (68.9:79.5)	76.0 (73.6:79.6)	
BMI	Mean ± SD	31.7 ± 8.2	31.1 ± 8.2	32.2 ± 8.3	0.35
	Median (95% CI)	30.3 (28.8:32.1)	29.9 (27.8:31.8)	30.9 (28.8:34.0)	
Waist (cm)	Mean ± SD	104.1 ± 16.1	101.6 ± 17.7	106.3 ± 14.4	0.08
	Median (95% CI)	105.5 (102.0:108.4)	102.0 (96.5:109.0)	107.0 (103.0:110.0)	
Fasting glucose (mg/dL)	Mean ± SD	95.8 ± 13.1	92.9 ± 9.8	98.3 ± 15.1	<0.01
	Median (95% CI)	94 (92:96)	93 (90:95)	96 (93:99)	
Fasting insulin (uIU/mL)	Mean ± SD	13.9 ± 8.2	13.3 ± 8.0	14.5 ± 8.5	0.50
	Median (95% CI)	12.1 (10.1:14.1)	11.6 (8.9:14.1)	12.3 (10.1:15.0)	
HDL Chol. (mg/dL)	Mean ± SD	57.5 ± 18.0	58.2 ± 20.9	57.0 ± 15.7	0.72
	Median (95% CI)	53.0 (51.0:55.0)	53.0 (50.5:57.5)	53.0 (50.0:60.7)	
LDL Chol. (mg/dL)	Mean ± SD	128.2 ± 31.7	130.4 ± 35.1	126.6 ± 29.4	0.59
	Median (95% CI)	122.0 (118.0:129.2)	124.0 (115.0:135.3)	121.0 (115.0:133.4)	
Triglycerides (mg/dL)	Mean ± SD	104.0 ± 57.6	92.0 ± 46.1	112.9 ± 63.7	0.05
	Median (95% CI)	91.0 (76.2:108.5)	74.0 (63.0:107.6)	105.0 (80.0:119.1)	
DBP (mmHg)	Mean ± SD	79 ± 12	78 ± 14	80 ± 10	0.28
	Median (95% CI)	80 (80:80)	80 (70:80)	80 (80:85)	
SBP (mmHg)	Mean ± SD	127 ± 21	122 ± 19	132 ± 21	<0.01
	Median (95% CI)	120 (120:130)	120 (110:120)	130 (123:140)	
25(OH)D (ng/mL)	Mean ± SD	20.2 ± 10.6	19.5 ± 10.0	20.8 ± 11.1	0.39
	Median (95% CI)	18.4 (16.8:20.0)	17.0 (15.0:20.0)	19.6 (16.8:22.0)	
Ca++ (mg/dL)	Mean ± SD	9.36 ± 0.42	9.31 ± 0.41	9.40 ± 0.43	0.32
	Median (95% CI)	9.30 (9.23:9.50)	9.30 (9.18:9.35)	9.45 (9.26:9.52)	

*P was calculated comparing mean values by t-test.

seasonality of vitamin D, we analyzed vitamin D status for each BMI category (normal, overweight and obese) according to high and low D-season (Fig. 3). In our population, 19% of women had normal weight, 31% were overweight and 50% were obese. All BMI categories demonstrated lower 25(OH)D mean values in low D-season respect with high D-season, with the lowest mean value (15.9 ng/mL) expressed in obese women in winter and the highest mean value (30.4 ng/mL) expressed in normal weight group in summer. Anova analysis demonstrated that differences in 25(OH)D mean values among BMI groups were statistically significant in both high D-season (F-ratio = 4.483, P < 0.01) and low D-season (F-ratio = 3.302, P < 0.01).

In order to evaluate whether there was a different response to sun irradiance between BMI subgroups, we performed linear regression analysis of 25(OH)D in high D-season in obese and non-obese women. Results indicated that both groups had a significant positive correlation of serum 25(OH)D concentration in the months April to September with a slope of 1.6 (obese group, F-ratio = 5.609, P = 0.02) and 1.7 (non-obese group, F-ratio = 4.538, P = 0.04) (Fig. 4). In order to obtain a whole picture of vitamin D status over the calendar year we performed a non-linear regression analysis using a sine curve and considering vitamin D values and months in two BMI subgroups, non-obese and obese subjects (Fig. 5). As expected, the best fitting model in non-obese women was a sinusoidal curve with a minimum value in March and a maximum in September. In obese subjects, the Y values in the modeled sine curve were always lower than those of curve from non-obese subjects.

4. Discussion

Hypovitaminosis D is a main concern in women because the age-related susceptibility to bone fragility. Fractures may occur in adult patients with severe vitamin D deficiency, but also in less severe vitamin D deficiency, in presence of more subtle mineralization defects, bone loss occurs leading to an increased risk for osteoporosis and fractures. Vitamin D status is related to bone mineral density, precipitates and exacerbates osteoporosis, causes the painful bone disease osteomalacia, and increases muscle weakness, which worsens the risk of falls and fractures. However, the role of vitamin D supplementation in osteoporosis and fracture prevention in elderly is still presently an area of controversy. The contradictory results in the literature could depend on many factors, including inclusion criteria, different doses of vitamin D, and the confounding role of calcium co-treatment, but also by the age of the patients. On the contrary, preventive intervention on vitamin D status could be effective in women of all ages, preserving bone health in older age. There is a need for large scale longitudinal trials on the effect of different doses of vitamin D with and without calcium on bone health of population in the different ages and that should also consider physiopathological conditions involved in maintaining low levels of vitamin D.

Our study indicates that high BMI is a strong predictor for low vitamin D in women of all ages. The sequestrating effect of fat tissue is so effective in lowering vitamin D that its effect prevails on seasonality, age and other covariables. At our latitude (42°N) serum level of 25(OH)D is strictly dependent on season, in fact, in winter, sun irradiation, poor in UVB, does not permit the synthesis of sufficient vitamin D in the skin and subjects, from October to March, manifest a progressive decline in serum concentrations of vitamin D accumulated in summer [18]. Because the time of clinic ascertainment of 25(OH)D is variable, seasonal variation should be always considered for understanding the real vitamin D status. Our data suggest that the highest seasonal difference in mean 25(OH)D concentration is about 10 ng/mL, in agreement with our and other studies (about 25 nmol/L [19]). This implies that winter 25(OH)D concentration in the range 20–30 ng/mL could increase to levels over 30 ng/mL after appropriate sun exposure in summer. Here we have confirmed the seasonality of vitamin D status, a phenomenon that is present also in obese subjects. When we analyzed data of

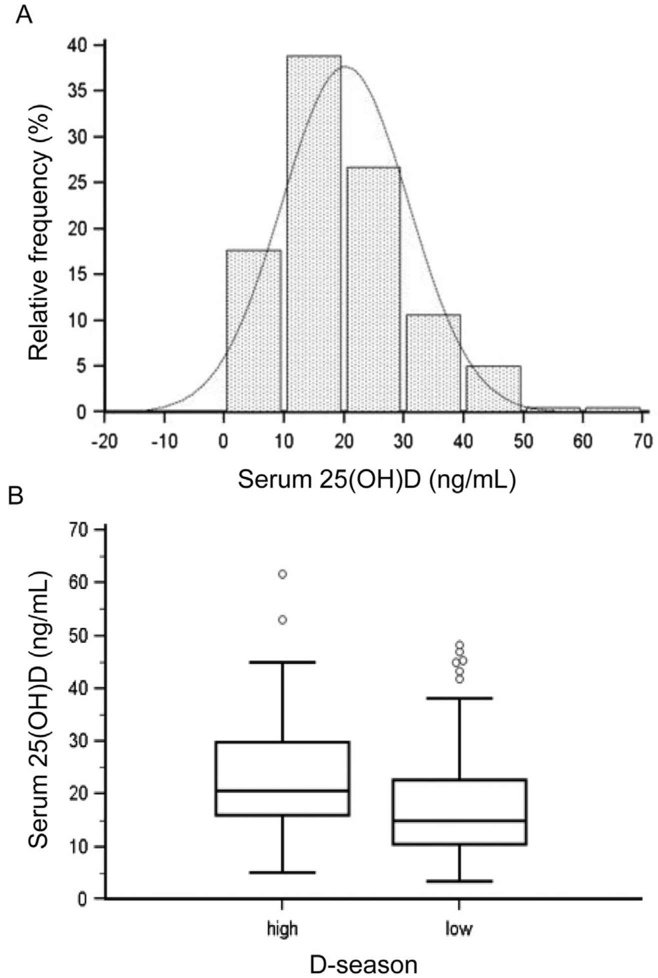

Fig. 1. Distribution of serum 25(OH)D considering all subjects. A) Serum 25(OH)D values were subdivided in 7 classes (from 0 to 70 ng/mL) and relative frequency (% vs all cases) for each class is shown. The line represents the best fitting normal curve obtained with measured 25(OH)D values. B) Serum 25(OH)D values were subdivided in two groups according to month in which the measure was performed. Box and whiskers diagram considering 25(OH)D values measured from April to September (high D-season) and values from October to March (low D-season) is shown.

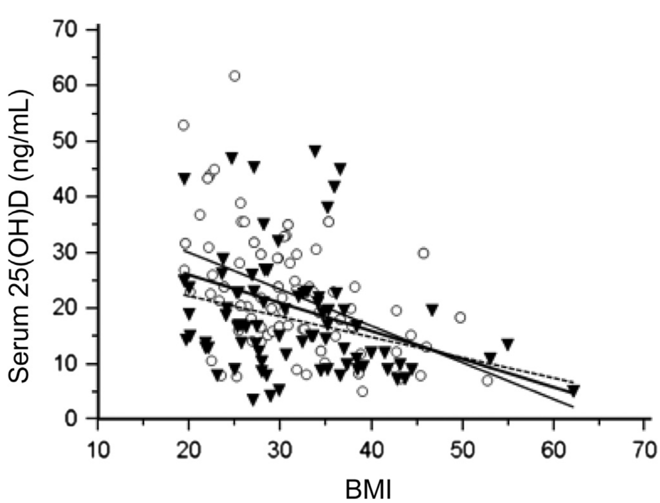

Fig. 2. Linear regression analysis using serum vitamin D (ng/mL) and BMI in all cases (thick line), in high D-season (circles and thin line) and in low D-season (triangles and dashed line).

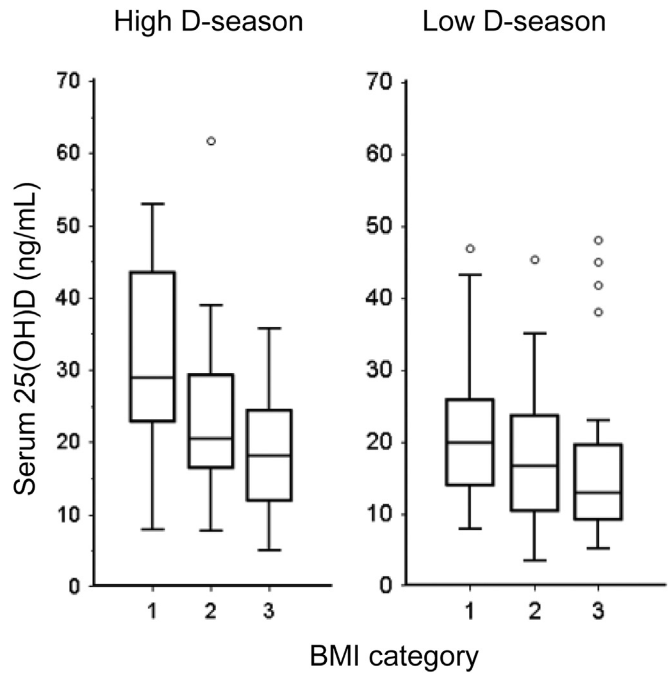

Fig. 3. Box and whisker graphs show median values of 25(OH)D in three BMI categories, normal weight (group 1, 18.5 ≤ BMI < 25), overweight (group 2, 25 ≤ BMI < 30) and obese (group 3, BMI ≥ 30), in high D-season (left) and in low D-season (right).

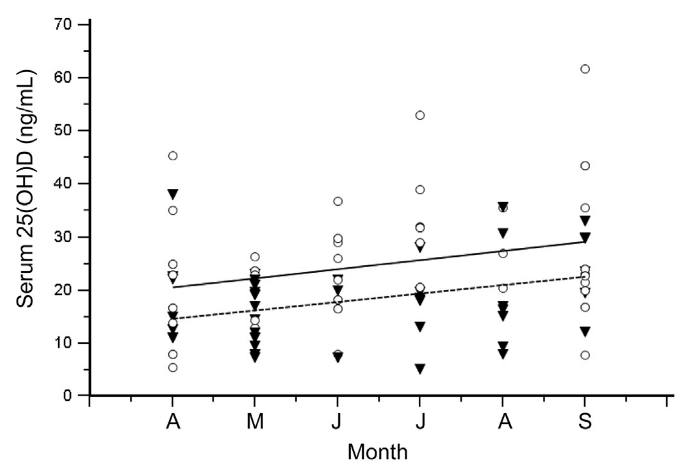

Fig. 4. Linear regression analysis was performed using serum vitamin D values (ng/mL) and months in which they were measured: white dots and solid line are representative for non-obese women; black triangles and dashed line represents values from obese women. Only values from April to September were used in the analysis.

serum 25(OH)D in summer, the slope of correlation with months was similar between obese and non-obese women. This conclusion is not obvious because other studies have suggested a possible difficulty in obese subjects in increasing serum 25(OH)D, especially in the elderly. We have to consider that women recruited in our study were free-living adults, and although several of them declared to be sedentary and to spend limited time outdoor, it is very probable that their vitamin D levels were positively influenced by the largely abundant UVB irradiance available from sun in summer. Although it was demonstrated the presence of an age-dependent reduction in vitamin D precursor in the skin, it cannot be excluded that the efficacy of the photosynthetic process could allow the maintenance of sufficient levels of circulating vitamin D levels also in the elderly. Accordingly, several studies have

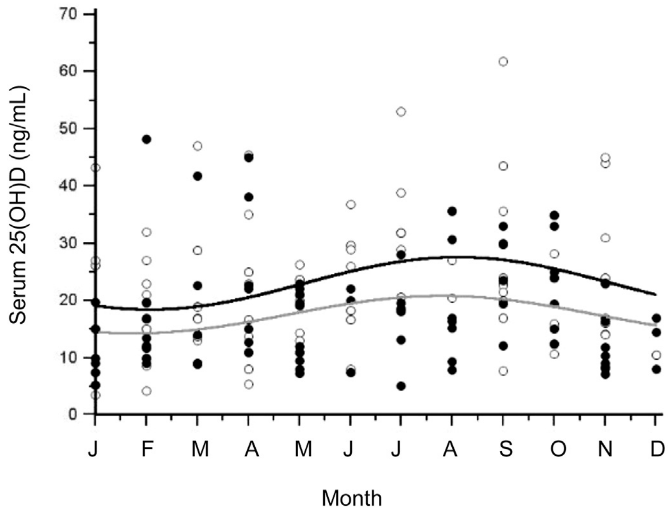

Fig. 5. Distribution of serum 25(OH)D values through months in which they were measured. Nonlinear regression curve for non-obese women (black dots and black line) and for obese women (white dots and gray line) were calculated.

suggested that UV irradiation resulted to have efficacy in the prevention of vitamin D insufficiency also in the aged subjects [20,21]. Obese subjects showed a sinusoidal trend in vitamin D status through the calendar year, just like the non-obese subjects. However monthly mean serum 25(OH)D values from obese women were always lower than the respective mean values from non-obese women. The resulting model is compatible with a reduced capacity of obese subjects in accumulating circulating 25(OH)D in summer.

In addition, when we applied to our population the linear regression model represented in Fig. 2 hypothesizing a BMI of 24, equal for all subjects (by mathematically eliminating obese and overweight subjects), we obtained a mean 25(OH)D value of 24.2 ng/mL (±9.8 ng/mL) that was a safer concentration able to contrast the obligate seasonal variance. This is a further demonstration of the importance of maintaining a normal BMI in order to avoid hypovitaminosis D. In our previous study we have demonstrated that at our latitude vitamin D status can be maintained sufficient by 2 h/week of sun exposure in summer in central hours of the day, however in real conditions an elderly male population who had higher serum 25(OH)D declared about 20 h/week or higher of outdoor activity [18]. Thus considering the difficulty in maintaining sufficient serum vitamin D concentration in general population, it is conceivable for obese persons the need for supplementation [22].

The cause of low 25(OH)D concentrations in obese individuals is poorly understood. Although the lipophilic property of vitamin D is well known, it is not clear whether its sequestration is controlled by metabolic mechanisms. The most parsimonious explanation, and confirmed by mathematical model, suggests that a simple volumetric dilution is able to explain 25(OH)D levels across the entire spectrum of body weight [23]. Our study is in agreement with the concept of the volumetric dilution, because the heterogeneity in our population, in particular for age, makes difficult to hypothesize the existence of alternative physiopathologic mechanisms.

However, we cannot exclude the presence of behavior-associated causes. Diet could play a significant role in differentially modulating vitamin D status in subjects who avoid consuming some foods [5], however this aspect is not important in our study because of the absence of vegetarians or vegans. In addition, paradoxically, a higher food intake in obese persons should determine a better vitamin D status. A frequently underestimated factor is the sun avoidance that could determine a reduced sun exposure in obese compared to non-obese women. In fact, although they have a larger skin area, obese women have psychologic difficulty in exposing their body, and tend to use long sleeved clothes also in summer, or to spend less time outdoor respect to non-obese women. The contribution of this psychologic aspect could not be measured in our study, but it is possible that it contributes anyway to render more solid the correlation between fat accumulation and hypovitaminosis D.

BMI is not a direct measure of a person's body fat composition: height and weight depend also on other variables than visceral fat deposition, including age, race and gender. Thus, some epidemiologic studies have questioned the idea of BMI as diagnostic tool and the use of the current cut-off for health risk stratification of the patients. Otherwise, BMI is the simplest and the most widely used parameter for measuring obesity and an extensive literature exists for a strong association between higher BMI and obesity-linked adverse health effects. Large studies have shown that the association between BMI and fat body percentage is good, but not perfect, and this is particularly true when BMI is lower than 25, mostly in men [24]. In our population 81% of women had a BMI higher than 25 and this could partially explain why in our study BMI was a strong predictor for body fat composition.

In summary, we found that BMI negatively correlated with serum 25(OH)D concentration, and it could be used as effective predictor of vitamin D status independently from age and season. In a population of women of all ages with increased risk of metabolic diseases and suffering from excess body weight, low vitamin D may play an important role in increasing pathologic manifestations such as insulin resistance, diabetes, metabolic syndrome and cardiovascular disorders. To counteract negative effects of vitamin D insufficiency, overweight and obese patients should be supplemented with adequate doses of vitamin D. In addition in these subjects monitoring of serum 25(OH)D could be recommended for correlating variation in vitamin D status with weight loss and seasonal effect linked to UV exposure.

Conflict of interest

All the authors declare no conflict of interest in connection with the current study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.02.024.

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