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Serum 25(OH)D seasonality in urologic patients from central Italy

Alessia Calgani [a], Marco Iarlori [b], Vincenzo Rizi [b], Gianna Pace [c], Mauro Bologna [c], Carlo Vicentini [c], Adriano Angelucci [a,*]

[a] Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università Degli Studi dell'Aquila, 67100 L'Aquila, Italy
[b] CETEMPS/Dipartimento di Scienze Fisiche e Chimiche, Università Degli Studi dell'Aquila, 67100 L'Aquila, Italy
[c] Dipartimento di Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'Ambiente, Università Degli Studi dell'Aquila, 67100 L'Aquila, Italy

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ABSTRACT

Hypovitaminosis D is increasingly recognized as a cofactor in several diseases. In addition to bone homeostasis, vitamin D status influences immune system, muscle activity and cell differentiation in different tissues. Vitamin D is produced in the skin upon exposure to UVB rays, and sufficient levels of serum 25(OH)D are dependent mostly on adequate sun exposure, and then on specific physiologic variables, including skin type, age and Body Mass Index (BMI). In contrast with common belief, epidemiologic data are demonstrating that hypovitaminosis D must be a clinical concern not only in northern Countries.

In our study, we investigated vitamin D status in a male population enrolled in a urology clinic of central Italy. In addition, we evaluated the correlation between vitamin D status and UVB irradiance measured in our region.

The two principal pathologies in the 95 enrolled patients (mean age 66 years) were benign prostate hypertrophy and prostate carcinoma. >50% of patients had serum 25(OH)D values in the deficient range (<20 ng/mL), and only 16% of cases had serum vitamin D concentration higher than 30 ng/mL (optimal range). The seasonal stratification of vitamin D concentrations revealed an evident trend with the minimum mean value recorded in April and a maximum mean value obtained in September. UVB irradiance measured by pyranometer in our region (Abruzzo, central Italy) revealed a large difference during the year, with winter months characterized by an UV irradiance about tenfold lower than summer months. Then we applied a mathematical model in order to evaluate the expected vitamin D production according to the standard erythemal dose measured in the different seasons. In winter months, the low available UVB radiation and the small exposed skin area resulted not sufficient to obtain the recommended serum doses of vitamin D. Although in summer months UVB irradiance was largely in excess to produce vitamin D in the skin, serum vitamin D resulted sufficient in September only in those patients who declared an outdoor time of at least 3 h per day in the previous summer.

In conclusion, hypovitaminosis D is largely represented in elderly persons in our region. Seasonal fluctuation in serum 25(OH)D was explained by a reduced availability of UVB in winter and by insufficient solar exposure in summer. The relatively high outdoor time that emerged to be correlated with sufficient serum 25(OH)D in autumn warrants further studies to individuate potential risk co-variables for hypovitaminosis D in elderly men.

1. Introduction

There is increasing concern about the incidence of hypovitaminosis D in general population. The meta-analysis of hundreds of worldwide cross-sectional studies revealed that over 80% of people suffer of vitamin D insufficiency [1]. Previous studies have demonstrated the existence of high-risk cohorts, including children, elderly and obese persons, so that plausible causes underlying the current epidemic of hypovitaminosis D are under investigation.

The natural acquisition of vitamin D is possible through two different routes: 1) by cutaneous UVB photosynthesis of vitamin D3 (cholecalciferol) from 7-dehydrocholesterol; 2) by dietary intake from foods that naturally contain animal vitamin D3 or vegetal vitamin D2 (ergocalciferol). In addition, fortified foods and vitamin D supplement use could represent other possible sources of vitamin D in some populations. Evolutive considerations and recent studies in indigenous populations of east Africa suggest that vitamin D is predominantly synthesized in our skin by UVB exposure and to a lesser extent derives from foods [2]. In addition, we may consider that a sufficient amount of vitamin D precursors is naturally available in few foods (fish, mushrooms) that are not particularly abundant in many diets. The measurement of serum 25(OH)D is routinely used in hospital laboratories for the analysis of vitamin D status. The association of serum 25(OH)D and UV radiation (UVR) exposure has been demonstrated in several epidemiological studies [3,4]. Two important demonstrations of this correlation are the dependence of serum vitamin D on seasonality and

* Corresponding author at: Dpt Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100 L'Aquila, Italy.
E-mail address: adriano.angelucci@univaq.it (A. Angelucci).

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on latitude [5–7]. Accordingly, during migration from tropical latitudes, *Homo sapiens* has been subjected to a strong selective pressure in order to adapt to changing geographical and climate conditions at low UVB irradiance, as clearly demonstrated by fascinating studies about evolution of human skin color [8]. In consequence of the strong association of vitamin D status with latitude, climate, skin color and lifestyle, it is necessary that causes of hypovitaminosis D should be investigated on geographical bases.

The discovery of the importance of vitamin D as regulator of Ca^{++} homeostasis and bone diseases (rickets and osteomalacia) is a well-known piece of the history of medicine [9]. The contemporary vitamin D insufficiency is characterized by the finding of biochemical evidence of low serum 25(OH)D, without obvious clinical signs or symptoms. The consequences of latent vitamin D insufficiency on adult skeleton are scarcely appreciated, but it is considered an important cofactor for osteoporosis, and fractures. The widespread tissue expression of vitamin D Receptor (VDR) and the pathologic phenotype expressed by VDR-null mice suggest that health impact of vitamin D deficiency is generally underestimated [10]. In agreement, recent data have unbelievably expanded our view about the role of hypovitaminosis D, including susceptibility to infective diseases, regulation of immune system and promotion of several cancers. Clinical studies have demonstrated that vitamin D deficiency is associated with an increased incidence rate of cardiovascular events, in particular with myocardial infarction and heart failure [11]. Observational studies have largely shown that low 25(OH)D levels are an independent risk factor for mortality in both the general population and in patients with chronic diseases [12,13].

In our study we aimed to examine the vitamin D status of an elder male population observed for urogenital illness at urology clinic and to investigate the relation of measured UVB irradiance at our latitude (central Italy) with serum seasonality of 25(OH)D. Results from this study could be important in establishing future recommendation in the attempt to avoid vitamin D insufficiency in the elderly population.

2. Materials & Methods

2.1. Patients and Location

The study was conducted in the cities of L'Aquila (42.35 N, 13.40 E, altitude 714 m), the location of our University, and of Teramo, the location of the urology department of our University (Mazzini Hospital), about 60 km NW of L'Aquila, both cities in Abruzzo region. Because Italy extends from 47° N to 35° N, geographical position of L'Aquila city is well described as central Italy. A total of 95 consecutive patients, routinely screened in our Urology Department for prostate diseases (benign hypertrophy, BPH or adenocarcinoma, CaP) or other urological diseases requiring surgical treatment or lithotripsy were enrolled between January and December 2009. The research has been carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospitals. Consent was obtained from all patients after full explanation of the procedure. Inclusion criteria were: male patients diagnosed for BPH, CaP or other urological diseases (such as lithiasis, tight frenulum, and penile prosthesis) in subjects between 50 and 80 years of age. The diagnosis of BPH or CaP was confirmed by histopathological analysis of the tissue obtained after prostate biopsy, transvescical (TV) retropubic adenomectomy or transurethral resection of prostate (TURP). No subjects suffered from any chronic debilitating or acute condition known to be associated with low vitamin D status (bone metabolism, hyperparathyroidism, malabsorption, chronic renal failure, liver insufficiency). No subject used vitamin D supplements. A detailed clinical status, with details on pharmacological therapies as well as comorbidities were obtained for each patient enrolled. The following clinic variables were collected: skin type (Fitzpatrick grade), body weight (kg), body height (cm), body mass index (BMI) calculated with the body weight divided by the square of the body height (kg/m^2). Obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2 and overweight as 25–29.9 kg/m^2. Fitzpatrick skin type was assessed by clinician-administered skin typing test (see Supplementary materials). Systemic blood samples were drawn from overnight-fasting patients and used to measure the following serum markers through routine analysis performed by our medical laboratory: testosterone, total cholesterol, triglycerides and vitamin D-25(OH)D. 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). Serum 25(OH)D > 30 ng/mL is considered to indicate sufficiency according to guidelines issued by Italian Health Ministry (Ministero della Salute). The definition of vitamin D deficiency is debated, and we adopted 20 ng/mL as cut-off value according to suggestions of international opinion leaders [14]. Patients enrolled in autumn were asked about their weekly outdoor behavior according to a simplified questionnaire (see Supplementary materials).

2.2. UVR Measurement

The coordinates of UVB and UVA pyranometers (Yankee Environmental Systems, Inc. Turners Falls, MA, USA) are 42.38 N, 13.31 E (elevation 683 m). Ultraviolet pyranometers are precision radiometers that measure global solar UVA (UVA-1 pyranometer, wavelengths from 320 to 400 nm) and UVB (UVB-1 pyranometer, wavelengths from 280 to 320 nm). Both UVA-1 and UVB-1 pyranometers use a fluorescent phosphor to convert UV light to visible light, which in turn is accurately measured by a solid state photodiode. Instruments are equipped with an internal temperature control system that maintains the efficiency of the optics and electronics. The output voltage of instruments was converted into physical units (W/m^2) of total UVA and UVB irradiance, by multiplying for a factor that takes in account the sensor performance for different SZA values. To convert the instruments output into the CIE (International Commission on Illumination)-defined erythemal irradiance in effective W/m^2, the signal voltage was multiplied by the specific SZA-dependent conversion factor [15]. SZA was calculated according to solar calculation resources by National Oceanic and Atmospheric Administration (NOAA, U.S. Department of Commerce, http://www.esrl.noaa.gov/gmd/grad/solcalc/index.html) considering the geographical coordinates of our pyranometers. The YES UVB pyranometer has a 5% uncertainty of spectral irradiance measurements [16]. The factors that influence the uncertainty could change over time [17]: for this reason a more conservative estimate of the uncertainty of 10% should be considered.

2.3. Mathematical Model of Serum Dose of Vitamin D

There is no consensus about the best estimation model of vitamin D production from the sunlight. The most cited model is based upon the “Holick's rule” affirming that exposing 1/4 of the skin surface to 1/4 MED (Minimal Erythema Dose) of sunlight will produce vitamin D equivalent to 1000 IU of vitamin D taken orally (standard vitamin D dose, SDD) [18]. MED is defined as the shortest exposure to ultraviolet radiation that produces reddening of the skin within 1 to 6 h with disappearing in 24 h. Holick's rule was recently discussed and integrated with important new considerations, and in particular with the biological effectiveness of the lamp used in the original work [19]. In order to apply Holick's rule to our data we calculated the SDD adopting the following formula:

$$SDD = k * SED * R * A \quad (1)$$

where k is a proportionality constant; SED is CIE weighted UVR dose of Standard Erythema Dose; R is the ratio of vitamin D-weighted irradiance (UV_{vitD}) and erythema-weighted irradiance (UV_{ery}); A is the fractional area of the exposed skin surface.