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ORIGINAL ARTICLE

Monthly fluctuations in 25-hydroxy-vitamin D levels in day and rotating night shift hospital workers

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Abstract

Purpose Epidemiological studies have suggested that indoor hospital employees, either day or night shift workers, are at high risk of metabolic and cardiovascular diseases. Interestingly, previous reports have also described a higher prevalence of vitamin D (25OHD) deficiency among these workers. However, few studies have determined the monthly variations in 25OHD levels in indoor hospital employees.

Methods To address this lack of knowledge, in 2018, during the periodic health surveillance checks at the Service of Occupational Medicine, we measured 25OHD levels in a group of indoor hospital workers (88 rotating night shift workers vs 200 day workers). Each participant received a single annual health surveillance check.

Results The mean levels of 25OHD were consistently below the lower limit of the normal range in both groups throughout the year. Only in the summer, day workers but not rotating night shift workers (mean 25.9 ± 11.3 ng/ml vs 23.1 ± 9.1 ng/ml; $p = 0.042$) showed levels significantly higher than those in the other seasons. This difference remained statistically significant even after correction for study covariates [$\beta = -1.649$ (CI − 0.283/− 3.482), $p = 0.039$]. A cosinor analysis confirmed that the difference in the 25OHD levels between groups was present later in the year.

Conclusions We found that relatively young healthy hospital workers, especially those with rotating night shifts, in the absence of significant metabolic risk factors, have a high risk of 25OHD deficiency/insufficiency. Because 25OHD deficiency may lead to a progression to more severe conditions such as osteoporosis or bone fractures, our results should be verified in larger cohorts including different ancestries.

Keywords Vitamin D deficiency · Night shift work · Osteoporosis

Introduction

The vitamin 25-hydroxy-vitamin D (25OHD) plays a critical role in the maintenance of normal blood levels of calcium and phosphorous [1], and therefore is crucial for bone health and many other biological processes [2]. Approximately 99% of 25OHD is transported in the circulation bound to binding proteins, mostly to Vit D binding protein (DBP) and, to a lesser extent, albumin. Although the cellular passive diffusion process can account for many of the biological effects of Vit D, some experimental evidences suggest that there are alternative pathways by which Vit D can be directed to a specific target tissue where they are taken up actively [3]. Megalin and cubilin are endocytic receptors present in skeletal muscle as well as in proximal tubule cells. They are involved in the reabsorption of vitamin D binding protein and the subsequent intracellular conversion of 25(OH)D to biologically active 1-25-dihydroxyvitamin-D3 [4]. Actually, vitamin D receptors mainly bind calcitriol, the activated form of vitamin D, which regulates the expression of a large number of genes across various tissues in the human body, affecting the immune, cardiovascular, musculoskeletal and nervous systems [5].

Many aging processes are regulated by 25OHD, and, although severe 25OHD deficiency does not preclude

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extreme longevity [6], it is a key modulator of oxidative stress and mitochondrial respiratory function [7–9].

Sunlight exposure is crucial for adequate serum 25OHD levels, and 25OHD-related problems may have become exacerbated by the emergence of a 24-h society. Changes in economic pressures and increasing production demands have resulted in work hours being spread across both day and night [10]. Thus, shift workers' behavioral and environmental cycles are typically misaligned relative to the endogenous circadian system, thus resulting in a predisposition to poor metabolic health [11, 12]. In the long term, this is detrimental to 25OHD related processes, thereby promoting several metabolic and bone disorders [13]. Deficiency in 25OHD has been reported among indoor and rotating night shift workers (r-NSW) such as healthcare professionals (e.g., nurses and physicians) [14]. However, few studies have been performed in this field, most of which have not considered monthly variations in 25OHD. To address this lack of knowledge, we investigated the associations between indoor hospital work and variations in 25OHD levels over the course of 12 months. In addition, we explored the annual 25OHD variation in relation to indoor hospital working status, comparing day workers and r-NSW.

Materials and methods

This was an observational study approved by the Independent Ethics Committee of the University Hospital PTV (Policlinico Tor Vergata) in Rome, Italy. The exclusion criteria included diagnosis of diabetes, liver disease, renal insufficiency or thyroid disorders; heart failure; coagulopathy; a history of any form of cancer; positive blood tests for HIV, hepatitis B, or hepatitis C; use of cholecalciferol medications or oral contraceptives, the intake of or other drugs interfering with vitamin D production/absorption or affecting its metabolism such as those contained in sunscreen creams within 6 months before the study. We recruited a group of volunteer hospital workers ($n = 295$) who underwent periodic health surveillance checks in 2018 at the Service of Occupational Medicine of University of Rome Tor Vergata. Participants were eligible if they had been working for a minimum of 2 years. We excluded seven hospital workers who were already taking cholecalciferol and/or calcium supplements, and the analysis was restricted to the remaining 288 workers. The participants received detailed information about the study protocol, and, after providing written consent, they underwent clinical examination and blood sample analysis after overnight fasting. Each participant received a single annual health surveillance check during the study period. We divided participants into two groups: (1) r-NSW ($n = 88$), working a shift schedule of four to seven 12 h nights per month, followed by 2 days off, and (2) day workers ($n = 200$) who had never worked night shifts. Of note, the employment status and environmental factors were similar for all study participants. The only different factors were educational attainment and income level. On this basis, we divided the study population into groups with lower and higher socio-economic status. To preserve the circadian rhythms of 25OHD, in the overall population, we obtained blood samples between 8:00 and 9:00 AM, after an overnight fast. In r-NSW, blood samples were withdrawn on the second day off.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured in participants in a sitting position after a 5-minute rest with a mercury sphygmomanometer. An average of three measurements was used to calculate systolic and diastolic blood pressure. Both 25OHD and intact parathyroid hormone (PTH) were measured with a chemiluminescent microparticle immunoassay (CMIA) test with an Architect Plus I2000 (Abbott©, Chicago, IL, USA) instrument. CMIA is not the gold standard for 25OHD and PTH measurement. However, the Biochemical Laboratory of Policlinic Tor Vergata is routinely screened with the International Quality Assessment Scheme (RIQAS), thereby ensuring the quality of our results. Therefore, following convention, we defined 25OHD deficiency as serum levels below 20 ng/ml, 25OHD insufficiency as serum levels 20–29.99 ng/ml, and normal values as serum levels above 29.99 ng/ml.

Statistical analysis

Patients' clinical characteristics are reported as the mean and standard deviation or frequencies and percentages for continuous and categorical variables, respectively. Each continuous variable was checked for normality of distribution with the Kolmogorov–Smirnov test. Unpaired *t* test was used to compare r-NSW and day workers for each of the reported variables. The Mann–Whitney test was used for variables with non-normal distribution. The significance of the difference in percentages between groups was evaluated with the X^2 test.

Univariate and multivariate linear regression analysis, using 25OHD level as the dependent variable, was controlled for the following study clinical covariates: age, sex, BMI, systolic and diastolic blood pressure, smoking and work status.

We also used cosinor analysis to investigate the seasonal variations in 25OHD levels between study groups. In this procedure, a cosine curve is fitted to the data on the basis of the least squares method, from which the MESOR (Midline Estimating Statistic of Rhythm; a mean value), amplitude (difference between the MESOR and the peak 25OHD concentration) and acrophase (time of the 25OHD peak) parameters were estimated [15].

A p value < 0.05 was considered statistically significant. All analyses were performed in SPSS version 19.0 for Windows.

Results

The main characteristics of the study population according to working status are summarized in Table 1.

In the overall study population, the mean 25OHD level was 25.16 ng/ml (range 4–58 ng/ml); we found 25OHD deficiency in 50% of the population and insufficiency in 29% of the population, whereas only 21% of participants showed sufficient levels of 25OHD. Interestingly, the 25OHD mean levels showed a significant association with age, BMI and r-NSW, whereas we did not find a significant relationship with systolic and diastolic blood pressure, smoking status and sex (Table 2). Of note, in all participants, the mean PTH level was 62.8 pg/ml (range 20–108 pg/ml), and a subtle tendency toward secondary hyperparathyroidism was observed. In agreement with these findings, we observed a significant correlation between lower 25OHD levels and higher PTH levels ($r = -0.466$, $p < 0.001$). Of note, creatinine mean levels were low and similar between the two groups (Table 1, $p = 0.148$) revealing a normal renal function in study population. Interestingly, creatinine levels did not show significant associations with 25OHD and PTH levels ($r = 0.092$, $p = 0.238$; and $r = 0.031$, $p = 0.559$, respectively). To avoid any possible confounding factors, we performed a multivariate regression analysis, including in the model only covariates significantly related to 25OHD levels in univariate analysis. The model indicated that 25OHD levels were significantly and independently associated with age and the summer season, and inversely correlated with BMI and r-NSW (Table 2). The model was highly significant ($F = 8.01$, $df = 2.9$, $p < 0.0001$) and explained 12.9% (adjusted R^2) of the variance in 25OHD levels.

Figure 1 shows the monthly variation in serum 25OHD levels in relation to working status. Of note, the mean serum vitamin D levels were frequently below the sufficiency threshold. A circannual rhythm of 25OHD level was detected in day workers ($p < 0.001$) but not in r-NSW

Table 1 Anthropometric and clinical characteristics of population according to study groups

	Daytime workers ($n = 200$)	Night shift workers ($n = 88$)	p
Population characteristics			
Age (years)	47.6 ± 9.8	44.7 ± 7.9	0.019
Female sex (%)	86	88	0.386
Systolic BP (mmHg)	129.1 ± 13.3	131 ± 16.9	0.223
Diastolic BP (mmHg)	78.6 ± 8.4	79.9 ± 9.1	0.101
BMI	23.2 ± 4.0	24.3 ± 5.4	0.065
Creatinine (mg/dl)	0.80 ± 0.15	0.77 ± 0.15	0.148
Active or previous smokers (%)	22	27	0.205
25 (OH) Vit D (ng/ml)	25.9 ± 11.3	23.1 ± 9.1	0.042
Parathyroid hormone (pg/ml)	62.0 ± 15.8	64.7 ± 17.4	0.202
Socio-economic level (lower/higher)	122/78	57/31	0.318

BP blood pressure, *BMI* Body Mass Index, *Vit D* vitamin D

Table 2 Univariate and multivariate analyses in overall study population for 25OHD levels (dependent variable)

	Univariate β coefficient (CI 95%)	p	Multivariate β coefficient (CI 95%)	p*
Age (y)	0.138 (0.006/0.269)	0.040	0.183 (− 0.009/0.275)	0.059
Sex (male)	− 1.766 (− 5.485/1.953)	0.351	np	
BMI	− 0.414 (− 0.685/− 0.142)	0.003	− 0.443 (− 0.701/− 0.184)	0.001
Systolic BP (mmHg)	0.017 (− 0.082/0.116)	0.736	np	
Diastolic BP (mmHg)	0.073 (− 0.064/0.210)	0.297	np	
Smoke (active or previous smokers)	− 0.276 (− 3.210/2.659)	0.853	np	
Working status (r-NSW)	− 1.039 (− 0.426/-2.153)	0.040	− 1.649 (− 0.283/− 3.482)	0.039
Season (summer)	2.084 (1.064/3.105)	0.002	1.949 (1.032/3.449)	0.009

The referent category of categorical variables is in brackets

BP blood pressure, *BMI* Body Mass Index, *Vit D* Vitamin D, *r-NSW* rotating-Night Shift Workers

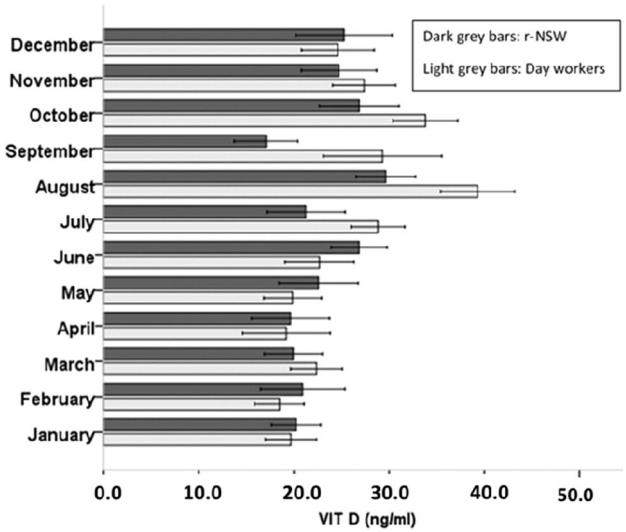

Fig. 1 Monthly fluctuaction of 25OHD levels according to working status

($p = 0.110$). A difference in MESOR had a trend toward statistical significance (daytime workers = 23.52 ng/ml vs r-NSW = 25.40 ng/ml, $p = 0.116$), similarly to the difference in circannual amplitude (daytime workers = 10.95 ng/ml vs r-NSW = 8.20 ng/ml; $p = 0.073$). Finally, we found a statistically significant difference in acrophase (1.53 vs − 0.01, $p = 0.002$).

Discussion

The prevalence of 25OHD insufficiency is high worldwide, even in regions with a long duration of sunlight exposure, such as southern Europe [16]. This prevalence may be due to various factors, such as aging of the population, clothing (for cultural reasons), use of sunscreen, diet poor in fat foods (rich in vitamin D, e.g., Mediterranean diet), and time spent indoors during both work and leisure activities [17]. In most available studies, indoor workers, regardless of geographical location, are consistently reported as the occupational group most likely to have 25OHD deficiency [14, 18].

Our results confirmed that indoor workers tended to have low levels of serum 25OHD [19], thus suggesting that the lack of sufficient sunlight exposure increases the risk of having low 25OHD levels. These data were corroborated by a subtle finding of secondary hyperparathyroidism in both study groups (Table 2). Various studies have mentioned the inverse correlation between PTH levels and 25OHD concentrations. However, in presence of inadequate amount of calcium intake, the 25OHD levels necessary to avoid secondary hyperparathyroidism risk increase [20]. In 2016, also the European Food Safety Authority (EFSA) wrote that the circulating value of PTH is not only dependent on the circulating levels of 25OHD, but also on those of calcium, also dependent on its daily food intake. Furthermore, in our population 25OHD level was significantly related to age on univariate analysis ($p = 0.040$). This result is in part unexpected because the incidence of hypovitaminosis D increases as age increases [21]. However, the study participants were relatively young (mean age = 45.6 ± 9.4) and this association became not significant on multivariate analysis. We also observed a high rate of 25OHD deficiency and insufficiency, which was more pronounced in r-NSW., After dividing the study population by working status, we found significantly higher mean serum 25OHD levels in day workers than in r-NSW ($p = 0.042$), although the groups had similar clinical and anamnestic characteristics. A cosinor analysis confirmed that night shift workers had slightly lower 25OHD levels than daytime workers overall, and this difference accounted for the much lower 25OHD values found in the summer. From July to September, most day workers had average 25OHD levels above 30 ng/ml, whereas most r-NSW did not. This finding is somewhat surprising because r-NSW workers with 2 days off after a night shift may potentially have longer sun exposure times, from 8 to 14 days per month, and this should increase 25OHD blood levels, because the major source of 25OHD in both children and adults is exposure to sunlight [22]. However, it is intriguing to speculate that the night shift behavior leading to an altered exposure to light at the proper solar spectrum for 25OHD synthesis might potentially be only one determinant of low levels of 25OHD. Actually, the biological clock is known to be desynchronized in r-NSW, and circadian misalignment may lead to shortened or disrupted sleep [23, 24]. Thus, poor quality of sleep in turn might influence 25OHD metabolism, because 25OHD receptors are widely distributed in different regions of the human brain, such as the hypothalamus, prefrontal cortex, central gray, substantia nigra and raphe nuclei, all of which have important roles in sleep regulation [25]. Finally, we cannot exclude a possible interaction between vitamin D and cortisol levels or stress-induced hormonal modifications, since it is very likely that rotating night shift hospital workers may suffer from high level of stress [26].

It is well known that serum levels of vitamin D vary throughout the different stages of life, depending on the season, latitude, degree of sun exposure, phototype and BMI. At present, a significant difficulty is encountered both in the field of research and in clinical practice due to analytical variability of the dosage of serum vitamin D levels. Today the dosage of 25(OH)D is commonly determined using an immuno-chemiluminescence method, which is characterized by an intra-assay and inter-laboratory variability of 10–20%. Similarly, also serum PTH evaluation has a different sensitivity threshold according to the generation of the used analytical method. Furthermore, mass spectrometric

methods, which nowadays serves as the gold standard for the quantitatively determination of 25(OH)D, do not necessarily produce comparable results, creating limitations for the definition of normal vitamin D status ranges [27]. Therefore, there is an urgent need for standardization/harmonization of these dosages both for a correct interpretation of clinical studies and for clinical practice.

Our study has several important limitations. First, each participant received a single annual health surveillance check during the study period; therefore, intra-individual fluctuations in 25OHD levels between day and night shift workers could not be examined.

However, the study participants were relatively young, apparently healthy and not taking any medication because they did not have any overt clinical disease. Second, although the clinical characteristics of r-NSW and day workers were comparable, the number of participants was unbalanced between the groups. Third, we did not account for other individual characteristics that might also have affected 25OHD values, such as total working hours (which varied between the two different job categories), leisure activities (indoor or outdoor), holiday sun exposure. Furthermore, we did not use appropriate and validated questionnaires on dietary habits (in particular considering also daily calcium intake). Additionally, we did not use the general population average vitamin D levels to which the study subjects belong. Moreover, the use of chemiluminescent microparticle immunoassay is another important weak point of this work, since CMIA is not the gold standard for 25OHD and PTH measurement. Finally, we did not include the menopausal status among the exclusion criteria. This may be a confounding factor because the majority of study participants were women. There is some evidence for involvement of 17 beta-estradiol in intestinal calcium absorption independent of 1,25-dihydroxyvitamin D3 level in animal models [28] and in women [29]. Nevertheless, our main finding clearly emphasizes that even relatively young healthy hospital workers, especially if working night shifts, in the absence of important metabolic risk factors, show subclinical metabolic defects that might be predictive of progression to more severe conditions such as osteoporosis or bone fractures. Future and perspective studies are warranted to understand if rotating night shift workers need to be treated with 25OHD.

Author contributions SR and LC contributed to the study concept, wrote the initial manuscript draft, performed the analyses, and read and corrected draft versions. MF and AM contributed to the conception and design of the trial, provided funding, read and corrected the initial manuscript, and corrected draft versions. AP, GGM, MC and MV read the paper and contributed significantly to editing and preparation of the final manuscript. All authors approved the final manuscript. SR and LC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no personal or financial conflicts of interest.

Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Furthermore, the study was approved by the Independent Ethics Committee of the University Hospital PTV (Policlinico Tor Vergata) in Rome, Italy.

Informed Consent The participants received detailed information about the study protocol, and, after providing written consent, they underwent clinical examination and blood sample analysis after overnight fasting.

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