Serious vitamin D deficiency in healthcare workers during the COVID-19 pandemic

Several reports suggest that vitamin D (VitD) deficiency could increase the predisposition to systemic infection, including respiratory tract infections and impaired immune response.[1–4] A recent meta-analysis demonstrated that VitD supplementation can reduce the risk of respiratory tract infections overall based on data from randomised controlled trials.[5] Moreover, an article reported a possible association of VitD level with cytokine storm and unregulated inflammation in elderly patients with COVID-19.[6] It supported the potential protective impact of VitD by enhancing the immune system and possibly reducing the risk of complications associated with cytokine storm and unregulated inflammation in patients with severe COVID-19. VitD is a lipid-soluble vitamin that acts as a ligand to the intranuclear receptor superfamily and plays a significant role in regulating between innate and acquired immunity.[1] 25-Hydroxy vitamin D (25(OH)D) is the major circulating form of VitD in humans and currently accepted as the best marker of VitD status.[7] To date, there are only a few reports focusing on nutritional status including 25(OH)D in healthcare workers (HCWs) during the COVID-19 pandemic.[8]

During the COVID-19 pandemic, we conducted a prospective observational study to evaluate several blood markers in HCWs at high risk of SARS-CoV-2 infection at the National Center for Child Health and Development in Tokyo, Japan.[7] Blood sampling was performed from the enrolled participants from 1 March 2021 to 5 March 2021, and all clinical laboratory testing of the blood including VitD, zinc and natural killer (NK) cell activity were examined at the SRL Hachioji Laboratory Complex, in Tokyo, Japan. 25(OH)D was measured using chemiluminescent enzyme immunoassay, and serum zinc level was determined using the colorimetric method. Also, chromium-51 release assay was used to assess the NK cell activity. We analysed the relationship between gender and VitD levels using the Fisher's exact test. In addition, the correlationship between VitD levels and age was calculated by the Pearson's product–moment correlation coefficient and

Table 1 Laboratory findings of the participants by sex

Variable	Male (n=87)	Female (n=274)	Standard value
Age (years) median, range	39 (25–60)	33 (22–67)	
NK cell activity (%) median, IQR range <18 (n, %) 18–40 (n, %) >40 (n, %)	20 (19.0) 1.0–50.0 37 (42.5%) 42 (48.3%) 8 (9.2%)	15 (14.0) 1.0–55.0 160 (58.4%) 105 (38.3%) 9 (3.3%)	18–40
Zinc (µg/dL) median, IQR range deficiency (n, %)	90 (16) 63–135 15 (17.2%)	88 (19) 51–123 76 (27.7%)	80–130
25(OH)D (ng/mL) median, IQR range deficiency* (n, %) severe deficiency† (n, %)	12.8 (6.6) 5.8–34.7 78 (89.7%) 22 (25.3%)	10.4 (6.4) <4–35.9 254 (92.7%) 132 (48.2%)	Deficiency <20 Severe deficiency <10
TP (g/dL) median, IQR range	7.4 (0.5) 6.7–8.3	7.4 (0.6) 6.4–8.3	6.7–8.3
Albumin (g/dL) median, IQR range	4.7 (4.0) 4.0–5.3	4.6 (0.4) 3.2–5.3	3.8–5.2
Fe (µg/dL) median, IQR range	101 (31) 18–184	86 (47) 20–251	Male 54–200 Female 48–154
HbA1c (%) median, IQR range	5.2 (0.4) 4.7–7.1	5.2 (0.4) 4.5–8.4	4.6–6.2
WCC (/µL) median, IQR range	5900 (1800) 2900–13 100	5700 (2100) 2300–11 500	Male 3900–9800 Female 3500–9100
Platelet (×10^4 /µL) median, IQR range	25.7 (5.9) 16.8–39.4	26.9 (7.0) 13.7–45.4	Male 13.1–36.2 Female 13.0–36.9
T-Cho (mg/dL) median, IQR range	204 (42) 145–282	198 (49) 123–336	150–219
HDL-C (mg/dL) median, IQR range	61 (19) 37–113	72 (20) 35–118	Male 40–86 Female 40–96
LDL-C (mg/dL) median, IQR range	122 (41) 73–207	103 (46) 39–274	70–139
AST (U/L) median, IQR range	20 (7) 12–57	18 (11) 11–204	10–40
ALT (U/L) median, IQR range	19 (13) 9–145	14 (7) 6–196	5–40
BUN (mg/dL) median, IQR range	14.0 (3.5) 8.0–26.9	12.4 (4.0) 5.4–24.0	8.0–22.0
Creatinine (mg/dL) median, IQR range	0.87 (0.15) 0.67–1.10	0.62 (0.11) 0.37–0.89	Male 0.61–1.04 Female 0.47–0.79
UA (mg/dL) median, IQR range	5.8 (1.5) 3.8–9.2	4.2 (1.1) 2.0–9.4	Male 3.7–7.0 Female 2.5–7.0

*25(OH)D <20 ng/mL,
†25(OH)D <10 ng/mL.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NK, natural killer; 25(OH)D, 25-hydoxy vitamin D; T-Cho, total cholesterol; TP, total protein; UA, uric acid; WCC, white cell count.

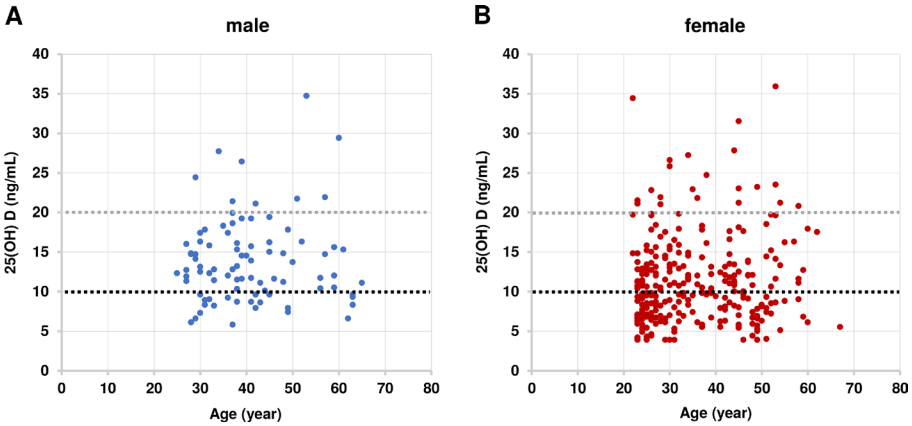

Figure 1 Scatter plot of 25-hydroxy vitamin D (25(OH)D) levels by sex. The median, IQR and range of the 25(OH)D levels were, respectively, 12.8, 6.6 and 5.8–34.7 ng/mL in the male healthcare workers (HCWs) (A) and 10.4, 6.4 and <4.0–35.9 ng/mL in the female HCWs (B). The dashed black lines indicate the thresholds of severe 25(OH)D level deficiency.

that between VitD levels and NK cell activity by the Spearman's rank correlation coefficient. All the statistical analyses were performed using SPSS V.22.0 software package (IBM). A two-sided p<0.05 was considered statistically significant. In the study, 361 HCWs were enrolled, of whom 274 (75.9%) were women. The median age was 35 years (range, 22–67 years). The measured blood markers are summarised in table 1. Most of the measured data were within their normal ranges in most cases except for the blood markers of decreased ability to protect against infections. The NK cell activity widely varied between the participants and was below the lower limit of normal in 42.5% (37/87) of the male participants and 58.4% (76/274) of the female participants. However, there was no correlation between the NK cell activity and 25(OH)D level (r=–0.047, p=0.374). The zinc level was deficient in 17.2% (15/87) of the male participants and 27.7% (76/274) of the female participants. Surprisingly, the 25(OH)D level was remarkably low in our study participants. The 25(OH)D level was deficient (<20 ng/mL) in 89.7% (78/87) of the male participants (figure 1A) and in 92.7% (254/274) of the female participants (figure 1B). In addition, 25.3% (22/87) of the male participants and 48.2% (132/274) of the female participants had severe 25(OH)D deficiency (<10 ng/mL). The rate of the female participants with severe 25(OH)D deficiency was significantly higher than that of the male participants (p=0.001). Additionally, there was no correlation between age and serum 25(OH)D level (r=0.094, p=0.074). A recent article from the UK showed that HCWs with VitD deficiency were more likely to develop COVID-19.[8] In the study population, HCWs in the black, Asian and minority ethnic groups were VitD deficient (70%), compared with Caucasians (30%).[8] A study targeting Japanese women aged 39–64 years reported a mean 25(OH)D level of 24.63 ng/mL and that 31.6%, 27.0% and 14.9% of women aged 39–49, 50–59 and 60–64 years, respectively.[9]

Approximately 90% of the participants in this study had VitD deficiency regardless of sex. This might have resulted from long-term indoor activities, both in medical care and daily life, in compliance with the state-of-emergency declaration over COVID-19 and our institutional infection prevention and control measures against COVID-19. From the article mentioned previously,[8] VitD deficiency was reported as an independent risk factor for developing COVID-19 seroconversion. Also, VitD potentially plays a significant role in preventing or alleviating acute respiratory tract infections including COVID-19, meanwhile, VitD levels could strongly account for variability COVID-19 severity: negative correlation between mean VitD levels and number of COVID-19 cases for one million population or outcomes/prognosis of patients with COVID-19.[1 2 8] Thus, clinical trials for investigating the efficacy of VitD supplementation targeting at-risk VitD deficient HCWs for developing COVID-19 are warranted. This study has several limitations, such as those of a single-centre observational study in Japan in a single period; lack of assessment of medical history, including COVID-19 and VitD-related diseases; lack of evaluation on the impact of seasonality on VitD level; and lack of information about lifestyle and VitD supplementation. However, given the decreasing ultraviolet absorption and possible contributions to treatment and prevention of COVID-19 of sun exposure and VitD supplementation[10] in addition to immediate COVID-19 vaccination, these measures should be considered to improve HCWs' lifestyles, particularly in VitD-deficient HCWs.

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