Short Communication

Serum 25-hydroxyvitamin D levels and psychological distress symptoms in patients with affective disorders during the COVID-19 pandemic

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ABSTRACT

Background. The COVID-19 pandemic has given rise to stress worldwide, especially in vulnerable people like those suffering from mental illness. This study aims to investigate the psychological distress perceived by a cohort of patients with Major Depressive Disorder (MDD) or Bipolar Disorder (BD) after a seven-week period of lockdown measures, and to analyze serum 25-hydroxyvitamin D [25(OH)D] levels as a potential predictor of distress severity.

Methods. Fifty-nine remitted MDD and fifty-three euthymic BD patients were enrolled. An online dedicated survey was administered to obtain lockdown-related information and to evaluate COVID-19 related distress by using the Kessler 10 Psychological Distress Scale (K10). Patients' medical records were reviewed to collect sociodemographic and clinical data, including serum 25(OH)D levels dosed in the three months preceding the outbreak. A multivariate general linear model was adopted to test the effect of factors of interest on psychological distress.

Results. In our sample (n = 112), 29 subjects (25.9 %) reported no likelihood of psychological distress, whereas 35 (31.2 %) and 48 (42.9 %) displayed mild and moderate-to-severe likelihood of psychological distress, respectively. Low serum 25(OH)D levels (p = 0.005) and MDD diagnosis (p = 0.001) specifically predicted the severity of psychological distress. Living alone during the lockdown, a longer duration of illness, and smoking habits were more frequently detected in subjects with COVID-19 related distress.

Conclusions. Low serum 25(OH)D levels and MDD diagnosis predicted an increased vulnerability to the stressful impact of the COVID-19 outbreak. Our results suggest that vitamin D may represent a biological factor mediating the psychological response to stress in individuals with affective disorders and provide further insight into tailoring intervention strategies.

1. Introduction

The ongoing COVID-19 pandemic and related containment measures imposed by governments, including self-isolation and social distancing, have largely affected mental health worldwide. Preliminary data from different countries highlighted increased levels of psychological distress among the general population (Vindegaard and Eriksen Benros, 2020; Xiong et al., 2020). Subjects with mental disorders showed to be even more consistently influenced by the COVID-19 epidemic and lockdown measures, reporting significant worsening of the clinical conditions and potentially higher risk for recurrence (Sani et al., 2020; Vindegaard and Eriksen Benros, 2020; Yao et al., 2020).

Vitamin D is a neuroactive steroid involved in brain development, synaptic plasticity, neuroprotection, neurotransmission, and neuro-immunomodulation (Groves et al., 2014). Vitamin D metabolites have been shown to protect neural integrity in brain areas implicated in the

pathophysiology of stress response and mood regulation, such as the prefrontal cortex, amygdala, and hippocampus (Groves et al., 2014; Wimalawansa, 2019). Also, vitamin D appears to play a role in the modulation of neuroinflammatory pathways, whose dysfunctions have been linked to both altered stress response and depression (Berk et al., 2013; Wimalawansa, 2019).

A growing body of literature suggests that vitamin D deficiency may represent an underlying vulnerability factor for several psychiatric disturbances, including major depressive disorder (MDD) and bipolar disorder (BD) (Anglin et al., 2013; Milaneschi et al., 2014; Patrick and Ames, 2015). Accordingly, low levels of vitamin D have been found in both MDD and BD patients (Belzeaux et al., 2015; Boerman et al., 2016; Cuomo et al., 2019), although the nature of this association as well as clinical and therapeutic implications are still debated (Jamilian et al., 2019; Okereke et al., 2020).

The link between hypovitaminosis D and response to stressful events, including possible future mental health outcomes, is less investigated. However, low serum levels of vitamin D have been associated with increased stress perception and worse clinical outcomes in response to traumatic events (Gwon et al., 2016; Chen et al., 2020; Terock et al., 2020).

To the best of our knowledge, no previous study on individuals with mood disorders has investigated the association between serum levels of 25-hydroxyvitamin D [25(OH)D] and psychological response to such a stressful large-scale event, like the ongoing COVID-19 outbreak. Therefore, we aimed to evaluate the psychological impact of the pandemic in a cohort of remitted patients affected by MDD or BD, and to analyze serum 25(OH)D levels as a potential predictive factor influencing the extent of psychological burden. We hypothesized that low serum 25(OH)D levels may predict increased psychological distress during the COVID-19 outbreak.

2. Materials and methods

2.1. Participants and procedure

Participants were enrolled among outpatients regularly referring to the Psychiatric Unit of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore of Rome. Inclusion criteria were: age 18–70; being Caucasian; DSM-5 diagnosis of MDD or BD (type I and II); euthymia for at least six months (Hamilton Depression Rating Scale - HDRS < 8; Young Mania Rating Scale - YMRS < 6); serum 25(OH)D levels measured between December 2019 and February 2020. To mitigate factors affecting 25(OH)D deficiency, we excluded individuals with chronic liver or renal diseases, severe conditions of malabsorption or malnutrition, with current alcohol or substance abuse, or taking vitamin D supplements. All enrolled patients had been under stable psychopharmacological treatment for at least six months and were routinely assessed through psychometric tests (including HDRS and YMRS) at baseline and follow-up visits. The final sample of 112 subjects may represent about 40 % of outpatients with mood disorders consecutively referring to our Unit during the three-month timeframe.

Participants were assessed through an on-line survey between April 27th and April 29th, 2020. This time-lapse was chosen to evaluate subjects' distress after a seven-week period of strict lockdown measures enforced by the Italian Government across the whole national territory (Decree of 9th March, 2020).

The survey was anonymous and data confidentiality was assured according to the European Survey Research Association (ESRA) guidelines. All participants completed the questionnaire online via EUSurvey. The study has been approved by the local Ethics Committee.

2.2. Data collection and psychometric assessment

A dedicated, self-report on-line questionnaire was administered to collect information on the patients' lockdown conditions (living alone, changes in work routines, working on the frontline), and to carry out the psychometric assessment. Sociodemographic (age, gender, educational level, occupation, marital status) and clinical data (psychiatric diagnosis, age of onset, duration of illness, hospitalizations, suicide attempts, current psychopharmacological treatment, lifetime history of chronic diseases, family history of psychiatric disorders, Body Mass Index (BMI), smoking habits, serum 25(OH)D levels) were extracted from the patients' medical records.

The Italian version of the Kessler 10 Psychological Distress Scale (K10) (Carrà et al., 2011) was used to assess the psychological impact of the COVID-19 outbreak. K10 is a 10-item questionnaire, based on a 5-point Likert scale ranging from 1 (never) to 5 (always), providing a global measure of distress, anxiety and depressive symptoms experienced in the most recent 4-week period. The total score may range between 10 and 50, and high scores indicate high levels of psychological distress. Consistently with previous validation studies (Andrews and Slade, 2001), we adopted the cutoff scores of >19 and >24 to detect the likelihood of mild and moderate-to-severe psychological distress, respectively.

2.3. Assessment of serum 25(OH)D levels and potential confounding factors

We retrospectively evaluated serum 25(OH)D concentrations in 112 patients. All 25(OH)D samples had been analyzed using chemiluminescence immunoassay (CLIA) and had been measured in nanograms per milliliter (ng/mL). As reported by the US Endocrine Society Clinical Practice Guidelines, vitamin D sufficiency is defined by serum levels of 25(OH)D ranging between 30 and 100 ng/mL (Holick et al., 2011). Potential confounding factors associated with serum vitamin D levels (age, BMI, smoking habits, medical comorbidities, and current pharmacotherapy) were included in the statistical analysis to control for possible biases. Further potential confounders, such as seasonality of blood sampling and sunlight exposure, were avoided by collecting 25(OH)D samples within the same timeframe.

2.4. Statistical analysis

To fit our aims, we have adopted a dual approach considering both K10 cutoffs and continuous total scores. In the first part of the analysis, we divided the sample into three groups according to the K10 cutoffs: 1) subjects without likelihood of psychological distress, 2) subjects with likelihood of mild psychological distress, and 3) subjects with likelihood of moderate-to-severe psychological distress. The one-way analysis of variance for continuous measures (ANOVA) and the chi-square test for nominal variables were used to compare factors of interest (sociodemographic characteristics, information on lockdown conditions, clinical data and serum 25(OH)D levels) in the three groups. The level of significance was set at $p < 0.05$.

In the second part of the analysis, a multivariate general linear model was adopted to evaluate the impact of risk factors on the gradient of psychological distress severity, considered as a continuum according to the K10 total scores. Multiple linear regression was used to predict the severity of psychological distress based on factors significantly associated with mild or moderate-to-severe psychological distress in univariate/bivariate analysis. Possible multicollinearity between the variables of interest was tested through the variance inflation factor (VIF) indicators. Statistical analysis was performed using SPSS v. 25 (IBM Corp., USA).

3. Results

In our sample (n = 112), 29 subjects (25.9 %) reported no likelihood of psychological distress, whereas 35 (31.2 %) and 48 (42.9 %) displayed mild and moderate-to-severe likelihood of psychological distress, respectively (overall mean K10 total scores = 22.5 ± 6.04). Results of

Table 1
Sociodemographic data, information on lockdown conditions, and clinical characteristics of the sample.

Characteristics (n, %; M ± SD)	Total	No psychological distress	Mild psychological distress	Moderate-to-severe psychological distress	χ^2 or F	df	p
Overall	112	29 (25.9)	35 (31.2)	48 (42.9)			
Sociodemographic characteristics							
Age (years)	47.2 ± 16.4	42.6 ± 13.0	45.4 ± 16.4	51.4 ± 17.6	3.200	2	**0.047**
Gender					0.829	2	0.661
Male	52 (46.4)	15 (51.7)	17 (48.6)	20 (41.7)			
Female	60 (53.6)	14 (48.3)	18 (51.4)	28 (58.3)			
Educational level (years)	14.6 ± 2.9	15.1 ± 3.1	14.0 ± 2.7	14.7 ± 3.0	1.159	2	0.320
Occupation					6.40	2	**0.041**
Employed	75 (67)	23 (79.3)	26 (74.3)	26 (54.2)			
Unemployed	37 (33)	6 (20.7)	9 (25.7)	22 (45.8)			
Marital status					1.58	2	0.454
Married	35 (31.2)	10 (34.5)	13 (37.1)	12 (25.0)			
Unmarried	77 (68.8)	19 (65.5)	22 (62.9)	36 (75.0)			
Information on lockdown conditions							
Living alone	29 (25.9)	5 (16.7)	4 (11.4)	20 (42.6)	10.9	2	**0.004**
Changes in work routines	47 (42.0)	16 (55.2)	14 (38.9)	17 (36.2)	3.03	2	0.220
Working on the frontline	2 (1.8)	0 (0.0)	0 (0.0)	2 (4.3)	2.85	2	0.240
Medical status							
Psychiatric diagnosis					6.60	2	**0.037**
Major Depressive Disorder	59 (52.7)	10 (34.5)	18 (51.4)	31 (64.6)			
Bipolar Disorder	53 (47.3)	19 (65.5)	17 (48.6)	17 (35.4)			
Age of onset (years)	37.0 ± 14.4	34.3 ± 9.7	37.2 ± 15.2	38.4 ± 16.1	1.056	2	0.353
Duration of illness (years)	9.9 ± 8.8	7.8 ± 6.4	8.2 ± 7.6	12.4 ± 10.2	3.247	2	**0.045**
Hospitalizations	30 (26.8)	9 (31.0)	5 (14.3)	16 (33.3)	4.10	2	0.128
Suicide attempts	7 (6.2)	2 (6.9)	2 (5.7)	3 (6.3)	0.0378	2	0.981
Current psychopharmacological treatment							
Antidepressants	77 (68.8)	19 (65.5)	24 (68.6)	34 (70.8)	0.239	2	0.888
Mood stabilizers	70 (62.5)	21 (72.4)	22 (62.9)	27 (56.3)	2.02	2	0.365
Antipsychotics	62 (55.4)	15 (51.7)	16 (45.7)	31 (64.6)	3.13	2	0.210
Sedative-hypnotics	20 (17.8)	2 (6.9)	7 (20.0)	11 (22.9)	3.32	2	0.190
Lifetime history of chronic diseases	20 (17.8)	4 (13.8)	4 (11.4)	12 (25.0)	3.18	2	0.204
Family history of psychiatric disorders	39 (34.8)	9 (31.0)	12 (34.3)	18 (37.5)	0.431	2	0.806
BMI	24.6 ± 4.5	24.8 ± 4.2	23.8 ± 3.8	25.1 ± 5.1	0.843	2	0.435
Smoking	41 (36.6)	14 (48.3)	16 (45.7)	11 (22.9)	6.45	2	**0.040**
Serum 25(OH)D levels	21.6 ± 12.2	28.2 ± 12.6	19.9 ± 10.9	18.8 ± 11.6	5.709	2	**0.005**
Psychometric assessment							
K10 results	22.5 ± 6.04	14.9 ± 2.7	22.5 ± 1.5	27.1 ± 4.9	125.19	2	**<0.001**

Significant results in **bold** characters. Abbreviations: M, mean; SD, standard deviation; df, degrees of freedom; χ^2, chi-squared test; p, statistical significance; F, value of variance of the group means; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; K10, Kessler 10 Psychological Distress Scale.

Table 2
Linear Regression.

Predictors	Estimate	SE	95 % Confidence Interval		t	p
			Lower	Upper		
Age	−0.0158	0.0405	−0.2586	0.1736	−0.390	0.697
Occupation	−2.2633	1.2185	−0.3588	0.0118	−1.857	0.066
Living alone	1.9343	1.2471	−0.0387	0.3164	1.551	0.124
Psychiatric diagnosis	−3.7815	1.1184	−0.4900	−0.1276	−3.381	**0.001**
Duration of illness	0.0839	0.0710	−0.0827	0.3257	1.181	0.241
Smoking	−0.5752	1.1538	−0.2265	0.1356	−0.498	0.619
Serum 25(OH)D levels	−0.1265	0.0443	−0.4271	−0.0769	−2.855	**0.005**

Significant results in **bold** characters. Abbreviations: SE, Size Effect; t, t statistic; p, statistical significance; 25(OH)D, 25-hydroxyvitamin D.

the univariate/bivariate analysis of sociodemographic characteristics, information on lockdown conditions and medical status, including serum 25(OH)D levels, are summarized in Table 1. The three groups differed in age, occupation, living alone during quarantine, psychiatric diagnosis, duration of illness, smoking habits, and serum 25(OH)D levels. Specifically, subjects displaying insufficient levels of 25(OH)D

were 14 (15.9 %), 32 (36.4 %), and 42 (47.7 %) within each group, respectively. According to the multivariate general linear model, low serum 25(OH)D levels and MDD diagnosis significantly predicted psychological distress severity (Table 2, Supplementary Figure 1). In particular, serum 25(OH)D levels were inversely associated with psychological distress severity. There was no significant multicollinearity in the model, as indicated by the fact that the VIF of all variables of interest was < 2.

4. Discussion

The psychological impact of the COVID-19 outbreak has rapidly become an issue of global interest, with an increasing concern over vulnerable people like those affected by mental health conditions. Hence, we conducted a survey to investigate the occurrence of psychological distress during the ongoing pandemic in a cohort of patients with mood disorders. Our findings indicate that 74 % of the sample was perceiving a form of psychological distress at the time of the study, nearly twice as much as what reported by K10 results among the Italian general population during an early phase of the epidemic (Moccia et al., 2020). Similarly, current evidence endorses the severity of the psychological impact of the COVID-19 outbreak among patients with affective disorders showing that post-traumatic stress, anxiety, and depressive symptoms are significantly higher than in healthy controls (Fiorillo and Gorwood, 2020; González-Blanco et al., 2020; Hao et al., 2020).

In our sample, an MDD diagnosis predicted a more severe

psychological distress during the COVID-19 pandemic, compared to BD.

Repeated evidence demonstrated alterations of the neuroendocrinal stress response in MDD patients, namely hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, which might represent a biological risk factor for sensitization to subsequent stresses (Heim et al., 2008). In fact, MDD patients seem to be at risk for greater psychological stress reactivity and for experiencing a recurrence when facing stressors, with a heightened sensitivity to social stress, especially if they have been exposed to traumatic experiences early in life (Stroud et al., 2011; van Winkel et al., 2015; Kim et al., 2020). Also, some reports suggest that remitted MDD patients, compared to euthymic BD, may perform poorer adaptive behaviors in the face of adverse events, that might impact on stress perception (Coulston et al., 2013).

Our findings indicate that low 25-hydroxyvitamin D serum levels were significantly associated with higher psychological distress in patients with mood disorders during the COVID-19 outbreak. Similar results were observed by Chen et al., who recently found a significant correlation between lower serum 25(OH)D and increased measures of psychosocial stress and poorer mental health in a large sample of young adults (Chen et al., 2020). However, further studies should aim at better clarifying this relationship.

The biological mechanisms through which vitamin D might modulate psychological distress are still unclear and require further investigations. Some evidence suggests that vitamin D may act as a neuroprotective agent from oxidative-stress damages and stress-induced inflammatory effects on the brain in rodent models, and that vitamin D deficiency exacerbates behavioral impairments caused by stress (Berk et al., 2013; Jiang et al., 2013; Groves et al., 2017). Interestingly, affective disorders are associated with chronic, low-grade inflammatory response, as well as with increased oxidative stress, which might conjointly contribute to neuro-progression (Berk et al., 2013). As a neuroactive hormone, vitamin D is also implicated in the metabolic pathways of the monoaminergic system, including serotonin and dopamine. The effects of stress seem to reduce brain monoamine synthesis and release, which may ultimately lead to increased anxious or depressive behavior (Lee and Han, 2019). Thus, combined stressful events and inadequate 25(OH)D levels may promote to some extent the onset of psychiatric symptoms and exacerbate mental diseases, particularly mood disorders (Patrick and Ames, 2015; Sedaghat et al., 2019). Several studies showed some beneficial effects of vitamin D supplementation in clinically depressed subjects with hypovitaminosis D (Parker et al., 2017; Jamilian et al., 2019). However, a large longitudinal randomized trial has recently shown that treatment with vitamin D_3, compared with placebo, does not result in a significant difference in the incidence and recurrence of depression or of clinically relevant depressive symptoms, nor in a change in mood scores (Okereke et al., 2020).

Some limitations to the generalizability of our results must be acknowledged. First, the study has a cross-sectional design and lacks longitudinal follow-up. Therefore, causality between 25(OH)D levels and stress response in patients with affective disorders cannot be unequivocally determined, and prospective studies with a larger sample size are needed to unravel causal inferences. Second, although multiple potential confounders were accurately investigated to estimate the correlation between vitamin D levels and psychological distress, additional confounding factors have not been collected (e.g., socio-economic status, physical activity, dietary habits, prolactin levels and other parameters of the phosphocalcic metabolism). Finally, the reliability of self-administered questionnaires may be partially biased.

5. Conclusions

Our data show that major depression and low levels of vitamin D may predict a higher load of psychological distress in patients affected by mood disorders when facing a stressful event. Future research should aim to determine whether vitamin D may be physiologically involved in

increased vulnerability to stress, revealing deeper relationships between systemic inflammation, monoaminergic modulation, and serum 25(OH)D levels. To this regard, potential benefits of vitamin D supplementation require further investigations. Mental health needs associated with the pandemic must be rapidly addressed, with a special focus on vulnerable people like those with mental disorders.

Declaration of Competing Interest

The authors report no declarations of interest.

CRediT authorship contribution statement

Marco Di Nicola: Conceptualization, Investigation, Methodology, Project administration, Formal analysis, Writing - original draft. **Luigi Dattoli:** Conceptualization, Data curation, Methodology, Project administration, Writing - original draft, Visualization. **Lorenzo Moccia:** Formal analysis, Writing - review & editing, Visualization. **Maria Pepe:** Data curation, Project administration, Writing - review & editing, Visualization. **Delfina Janiri:** Formal analysis, Writing - review & editing, Visualization. **Andrea Fiorillo:** Supervision, Validation, Visualization. **Luigi Janiri:** Supervision, Validation, Visualization. **Gabriele Sani:** Methodology, Supervision, Validation, Visualization.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104869.

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