Depression and covid 19-Vit D

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Depression in female medical students; physiological basis and impact of Vitamin D deficiency during home isolation during COVID-19

Abstract: Depression is one of the common psychological disorders, and it is commonly to be found in females. There are many causes of depression e.g. genetic, environmental, social etc. On the other hand, many theories explain the physiological basis of depression. Interestingly social isolation is one of the causes of depression. During COVID-19 social isolation leads to increase the cases of depression which could be due to quarantine or decrease exposure to vitamin D. Data collection showed that the cases of depression increased during COVID 19 from quarantine even there is no family isolation which could be due decease exposure to sun and decreased vitamin D formation.

Depression is the most common psychiatric disorder reported in most of the community based studies. It is also reported as one of the most common psychiatric disorder in females. Life events during the period preceding the onset of depression play a major role in depression. Studies on women have also shown the importance of identifying risk factors for development of depression [1].

Depressive illness comes in different forms, just as many other illnesses:

i. Major depression is manifested by a combination of symptoms that interfere with the ability to work, sleep, eat and enjoy once pleasurable activities.

ii. Dysthymia, a less severe type of depression, involves long-term, chronic symptoms that do not disable, but keep you from functioning .

Depressive disorders are considered mostly from the general predisposing factors for depression-related deaths due to suicide and stroke, depression has the third highest global burden of disease.[2]

Depression is growing in overall disease burden in Egypt and around the world; it is predicted to be the leading cause of disease burden by 2030, and it is already the leading cause in women worldwide. In Egypt , major depressive disorder showed a 37% of phycological disorders. [3]
A recent meta-analysis showed that depression affects approximately one third of medical students worldwide [4]

Many factors can be a leading cause of depression in females. In this review we are going to summarize the causes of depression and the physiological basis for explanation of these causes.

Causes of depression :

University students face various stressors such as academic requirements, time pressure and social adjustments, and medical students in particular, may face additional challenges such as the large workload .

A study was done on first-year medical students in which 141 students were included and completed measures of anxiety, depression, hope, and spiritual meaning at three time points during the first year were done. Buccal samples were utilized to genotype each individual at the s/l variant in the promoter region of the serotonin transporter gene (5-HTTLPR). A subset (n = 91) completed a measure of recent stressors. Mean levels of depression increased during year one of medical school. Presence of the s/s genotype in the promoter region of the 5-HTT gene was associated with greater increases in depression, but only in association with higher numbers of recent stressors. Spiritual meaning and hope were found to counteract genetic susceptibility to stress-related depressive symptoms in the more vulnerable s/s group. [5]

Another study was done on depression among medical students in Saudi medical colleges: a cross-sectional study. Patient Health Questionnaire-9 (PHQ-9) was used for screening and associated with sociodemographic characteristics. A total of 2,562 medical students from 20 universities were recruited into this study, and 1,572 (61.4%) of the participants were females and 990 (38.6%) were males. Depression symptoms are found to be associated with college years with unstable living conditions and smoking status ($P<0.05$) [6].

An old study was performed on 304 first- and second-year medical students were prospectively assessed for depression with a monthly Beck Depression Inventory (BDI). Students scoring above nine on the BDI and a control group were then interviewed with the NIMH Diagnostic Interview Schedule. The incidence of major depression or probable major depression by DSM-III criteria during the first two years of medical school was 12%. The lifetime prevalence was 15%, three times greater than the rate in the general population. An episode of depression prior to medical school was much more common among the depressed students (69 vs. 8%, $P < 0.001$) as was a

family history of treated depression (46 vs. 21%, $P < 0.025$). The elevated rate of depression during medical school does not appear to be a result of the medical school experience alone. Rather, it suggests a positive bias of unknown nature in the selection of students predisposed to depression [7].

A cross-sectional study was conducted on 494 medical students with clinical experience at HMU from November 2015 to January 2016. Random sampling technique to select and invite students to complete a questionnaire including demographic characteristics, Patient Health Questionnaire 9 (PHQ-9), Academic Motivation Scale (AMS), and International Physical Activity Questionnaire Short Form (IPAQ). Results showed (78.8% response rate), the prevalence of self-reported depression was 15.2%, and suicidal ideation was 7.7%. Self-reported depression was significantly associated with perceived financial burden, physical inactivity, being senior student, perceived negative influence of night shifts, and non-self-determined motivation profile. Suicidal ideation was significantly associated with perceived financial burden and non-self-determined motivation profile [8].

The prevalence of depression among medical students of Saudi Arabia ranged from 30.9% to 77.6% with a mean prevalence of 51.5%. Depression severity was evaluated by various questionnaires, the extracted data revealed that medical students tend to have moderate to severe depression to a greater extent than mild depressive symptoms (33.27% vs 29.9%). The findings suggest a high incidence of depression among medical students and the influence of associate sociodemographic factors. Females are considered to be at a higher risk of depression. First-year medical students are the most susceptible to develop depressive symptoms. Smoking is strongly

associated with depression severity. Marital status, eating habits, usage of stimulants, and sleep disturbances are within significant findings of our review study [9].

There are many theories that could explain the physiological basis of stress:

HPA axis theory:

A- Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. This hormone induces the secretion of pituitary corticotropin, which stimulates the adrenal gland to release cortisol into the plasma. The physiologic response to stress is partly gender-specific: women show generally greater stress responsiveness than men, which is consistent with the greater incidence of major depression in women [10]. Moreover, men show greater cortisol responses to achievement challenges, whereas women show greater cortisol responses to social rejection challenges [11]. Subjects with MDD do show abnormalities of that axis and of the extrahypothalamic CRH system. Altered stress hormone secretion appeared to be most prominent in depressed subjects with a history of childhood trauma [12]. Elevated cortisol may act as a mediator between major depression and its physical long-term consequences such as coronary heart disease, type II diabetes, and osteoporosis [13]. This theory is going with that always medical students especially females are always under stress and elevated cortisol levels due to stressful medical school life as exams, quizzes , assignments and also competition between different medical school colleagues and this open the door for stress and depression.

-Inflammatory theory : Sickness behavior" as a result of an activation of the inflammatory response system shares many symptoms with depression, including fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Sickness is mediated by pro-inflammatory cytokines such as interleukin-1α, tumor necrosis factor-α, and interleukin-6, which activate the HPA axis and impair the central serotonin system [14]. Continuous exposure to stress in the case of these female medical school students lowers the immune system and increased liability for infections and elevation of inflammatory mediators .

Disturbance of Neurotransmitters theory:

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression) [15]. There is also evidence for abnormalities of serotonin receptors in depression, with the most solid evidence pointing to the serotonin-1A receptor, which regulates serotonin function [16].

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of depression, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients [17]. In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1 adrenergic receptor density have been found in the brains of depressed suicide victims post-mortem [18].

On the other hand, in the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover [19]. Moreover depressive-like behaviors and decreases in hippocampal BDNF levelsreductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression [20].

Here is to say that medical students exposed to stress which causes disturbance in the brain neurotransmitters as well-known from previous researches. This disturbances as mentioned before is one of the theories of cause of development of depression.

Sleep disturbances Theory : A study was performed on the relation between Sleep disturbance and daytime fatigue are development of depression, they found that depression is over-represented among populations with a variety of sleep disorders. Longitudinal studies have consistently identified insomnia as a risk factor for the development of a new-onset or recurrent depression, and this association has been identified in young, middle-

aged, and older adults [21]. Studies have also observed that the combination of insomnia and depression influences the trajectory of depression, increasing episode severity and duration as well as relapse rates. Fortunately, recent studies have demonstrated that both pharmacological and nonpharmacological interventions for insomnia may favorably reduce and possibly prevent depression. sleep problems were the most, prevalent, (13.6%), and those with sleep problems had the highest, relative odds (7.6 times) of developing a new-onset major depressive episode during the next year compared with those without sleep problems. Sleep problems also identified 47% of individuals who develop depression in the following year, more than any other depression symptom [22]

Sleep disturbance leads to disturbance in the physiological biological circadian rhythm and disturbance of corticosteroids secretion that could be one of the causes of depression [23]. In healthy young subjects, moderate changes in the timing of the sleep-wake cycle had specific effects on subsequent mood. In this review we can conclude that medical students are mostly having sleep disorders that could be one of the causes of depression.

The relation between COVID -19 and depression:

The COVID-19 pandemic is imposing a profound negative impact on the health and wellbeing of societies and individuals, worldwide. One concern is the effect of social isolation as a result of social distancing on the mental health of vulnerable populations, including older people. Within six weeks of lockdown, a study on healthy older people

living in London, to investigate the impact of COVID-19 and associated social isolation on mental and physical wellbeing. The sample was drawn from CHARIOT, a register of people over 50 who have consented to be contacted for aging related research. A total of 7,127 men and women were included in the study (mean age=70.7 [SD=7.4]) Participants were asked about changes to the 14 components of the Hospital Anxiety Depression scale (HADS) after lockdown was introduced in the UK. A total of 12.8% of participants reported feeling worse on the depression components of HADS (7.8% men and 17.3% women) and 12.3% reported feeling worse on the anxiety components (7.8% men and 16.5% women). Fewer participants reported feeling improved (1.5% for depression and 4.9% for anxiety). Women, younger participants, those single/widowed/divorced, reporting poor sleep, feelings of loneliness and who reported living alone were more likely to indicate feeling worse on both the depression. There was a significant negative association between subjective loneliness and worsened components of both depression and anxiety. Results may inform targeted interventions and help guide policy recommendations in reducing the effects of social isolation related to the pandemic, and beyond, on the mental health of older people [24].

Here in this review we are trying to intermingle another hidden factor which is the role of vitamin D and development of depression.

Vitamin D is well known for its role in promoting bone health and regulating vital calcium level. Scientists have now linked this fat-soluble nutrient's hormone like activity to a number of functions throughout the body, including the workings of the brain [25]. Nowadays it is well known that there are receptors for vitamin D throughout the central nervous system and in the

hippocampus. Furthermore, the VDR is also expressed in the prefrontal cortex, cingulate gyrus, basal forebrain, caudate/putamen, thalamus, substantia nigra, lateral geniculate nuclei, hypothalamus, and cerebellum.[26] Interestingly, vitamin D activates and deactivates enzymes in the brain and the cerebrospinal fluid that are involved in neurotransmitter synthesis and nerve growth. In addition, animal and laboratory studies suggest vitamin D protects neurons and reduces inflammation [27]

Vitamin D a lipid soluble vitamin, also known as sunshine vitamin synthesized in skin in the presence of sunlight [25]. This vitamin strongly known for its role in calcium and bone metabolism and maintaining bone integrity, but also it has more functions than just that [28]. It has been linked to some disorders throughout the body such as cardiovascular disease, cancer, stroke, metabolic disorders including diabetes [29].

The primary source of vitamin D is sunlight; it is also obtained from a few foods such as oily fish and fortified margarine. Vitamin D carries a cholesterol backbone and has steroid-like effects. It is the fat-soluble hormone that plays an essential role in brain health [30].

Malnutrition can be a causative factor not only for vitamin D deficiency, but for other fat and water-soluble vitamins that are important for neurocognitive function. Recent reviews reported that children, as well as young, middle-aged, and older adults are at risk for vitamin D deficiency worldwide [30, 31].

Some studies conducted recently shows the effect of vitamin D on early life brain development. In May 2018, a study conducted by Yates et al. shows that deficiency of vitamin D in maternal and offspring shows some disabilities in early life including learning and memory problems and grooming behaviors [26].

Vitamin D receptor (VDR) is a nuclear steroid receptor through which it performs its functions in the brain. It has been found that synthesis and destruction of vitamin D occur in the brain. Vitamin D is increasingly recognized as a necessary neuro-steroid with various actions in the brain [32]. It has been reported that VDRs and the regions of serotonin receptors and tryptophan hydroxylase, have a relationship with depression [33].

Circulating 25(OH) vitamin D crosses the blood-brain barrier and enters glial cells and neuronal cells to be converted into 1,25(OH) 2 D, which is the active form of vitamin D [27].

On the other hand, a study did not find any association between vitamin D levels, polymorphism of vitamin D receptor, and depression [34]. In the future, more studies are needed to show the mediatory role of genes in vitamin D impact.

In November 2017, Kesby JP et al. conducted a study showing the effect of vitamin D on both widespread neurotransmitter changes (glutamine/noradrenaline) and regionally selective neurotransmitter changes (dopamine/serotonin). It concluded that developmental vitamin D deficiency leads to these brain changes. Vitamin D is a potent antioxidant through inhibition of free radical generation by nitric oxide synthase and gamma-glutamyl transpeptidase [35].

Hypothesis argues that vitamin D reduces the increase in neuronal levels of calcium (CA +2) that are driving depression. Vitamin D plays a role in maintaining the expression of the CA 2+ pumps and buffers that reduce CA 2+ levels, which may explain how it acts to reduce the onset of depression [36].

Continuous stress could lead neuronal cell deaths m and this could develop depression. Here comes the role of vitamin D that play a pivotal role in neuronal differentiation and maturation via control

of the synthesis of neurotrophic agents such as nerve growth factor (NGF) and glial cell-line-derived neurotrophic factor (GDNF). Nerve growth factor is important for the growth, maintenance, and survival of certain target neurons and also has been implicated in maintaining and regulating the normal functioning [37].

We concluded from these previous information that Vitamin D is important in brain function and regulation its neurotransmitters release. We can depict that vitamin D deficiency leads to disturbance in brain function and could lead to many disorders in mental diseases as depression.

During COVID 19 pandemic home quarantine was world wide leading to social isolation which was a cause of depression. A study was done to investigate the association between social isolation and loneliness, how they relate to depression, and whether these associations are explained by genetic influence. Data from the age-18 wave of the Environmental Risk Longitudinal Twin Study, a birth cohort of 1116 same-sex twin pairs born in England and Wales in 1994 and 1995. Participants reported on their levels of social isolation, loneliness and depressive symptoms. .They entered simultaneously in a regression analysis, loneliness was more robustly associated with depression. Similar degrees of genetic influence on social isolation (40 %) and loneliness (38 %), and a smaller genetic influence on depressive symptoms (29 %), with the remaining variance accounted for by the non-shared environment. Genetic correlations of 0.65 between isolation and loneliness and 0.63 between loneliness and depression indicated a strong role of genetic influences in the co-occurrence of these phenotypes the study concluded that socially isolated young adults do not necessarily experience loneliness. However, those who are lonely are often depressed, partly because the same genes influence loneliness and

depression. Interventions should not only aim at increasing social connections but also focus on subjective feelings of loneliness. [38]

On the other hand depression seen during COVID 19 may be due to decreased exposure to the sun and decreased Vitamin D formation leading to depression as mentioned before that vitamin could be a key to open the gate for depression.

Conclusion : Depression among medical students during COVID 19 could be social isolation or decreased exposure to vitamin D and this requires further investigations.

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