Establishing a Relationship among Vitamin D, Depression, and Aging: A Review

By
Nushaiba Binte Hasan
19146025

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Declaration

It is hereby declared that.

1. The thesis submitted is my own original work while completing a degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Nushaiba Binte Hasan
19146025

Approval

The thesis titled "Establishing a Relationship among Vitamin D, Depression, and Aging: A Review" submitted by Nushaiba Binte Hasan (ID 19146025) of Spring, 2019 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Tanisha Tabassum Sayka Khan
Lecturer
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

Vitamin D deficiency has been linked to various health conditions, including depression and age-related disorders. The role of vitamin D in the prevention of depression and accelerated ageing has gained attention in recent years. Research suggests that maintaining adequate vitamin D levels may have a protective effect on mental health and ageing-related processes. The review examines existing research to determine the extent of the relationship between vitamin D status, depressive symptoms, and the ageing process. It also explores the potential mechanisms and clinical implications, emphasizing the necessity for further investigation and interventions to promote mental well-being people.

Keywords: Depression, Vitamin D, Ageing, Telomere length

Dedication

I would like to dedicate this thesis to my parents, who have given me a wonderful life with all kinds of privileges of education. Along with that, I would like to dedicate this thesis to my supervisor for her immense support and unconditional help.

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List of Acronyms

HPA	Hypothalamic-pituitary-adrenal
TL	Telomer length
MDD	Major Depressive Disorder
PDD	persistent depressive disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DMDD	Disruptive Mood Dysregulation Disorder
ODD	Oppositional defiant disorder
RDoC	Research Domain Criteria
OECD	Organization for Economic Cooperation and Development
CM	Child management
HDRS-17	The Hamilton Depression Questionnaire
BDI-II	Beck Depression Inventory
IDS-SR	Inventory of Depressive Symptomatology-Self Report (IDS-SR)
5HT2A	"5-HT" = 5-hydroxytryptamine
TPH	Tryptophan hydroxylase
COMT	Catechol-O-methyltransferase protein
GEE	Generalized estimating equation.
HAM-D	Hamilton Rating Scale for Depression
BAT	Behavioral activation therapy
CBT	Cognitive behavior therapy
IPT	Problem-solving therapy, interpersonal psychotherapy
GPs	General practitioners
DBS	Deep brain stimulation
PD	Parkinson's disease
TRD	Treatment-resistant depression
sACC	Safety and efficacy of electric stimulation
CYP2R	Cytochrome P450 enzyme
25(OH)D	25-hydroxyvitamin D

$(1,25(OH)_2D)$	1, 25-dihydroxy vitamin D
EFSA	European Food Safety Authority
VDRs	Vitamin D receptors
CNS	Central nervous system
BDNF	Brain-derived neurotrophic factor
NGF	Nerve growth factor
(NT)-3	Neurotrophic factor
TrK	Tropomyosin-related kinase
p75NTR	Neurotrophic receptor p75
CES-D	Centre for Epidemiologic Studies-Depression scale
NHAPC	Nutrition and Health of the Ageing Population in China
RCT	Randomized controlled trial
LLD	Late-life depression
HD	Huntington's disease
RNS	Reactive nitrogen species
ROS	Reactive oxidative species
LTL	Leukocyte telomere length

Chapter 1 Introduction

1.1 Background

Particularly in primary healthcare, depression is still treated as a separate clinical entity. Yet, the proper therapy of depression depends on the subtyping of depression. The clinical definition for a major depressive disorder includes the presence of five or more symptoms over a two-week period (Benazzi, 2006). 350 million people experience depression globally, making it the fourth-leading reason of illness burden and the main source of disability. The efficacy of conventional depression treatment is called into question, though, as meta-analyses of drug therapies show slight variation from placebo, after a month, comparisons of actual and sham electroconvulsive therapy interventions reveal minimal change, while there is limited encouragement regarding the application of specialized cognitive therapies. Hence, researchers looked at the data supporting alternative depression management strategies. The proof supporting the efficacy of supplementation of vitamin D was accumulated because there is a well-documented link between depressive illnesses and Vitamin D insufficiency, which results from a deficiency of sun exposure. Because vitamin D is a particular secosteroid hormone generated mostly by photosynthesis, staying indoors and escaping the sun might result in a deficiency (25- hydroxy vitamin D < 50 nmol/L). Billions of people worldwide suffer from vitamin D insufficiency, which is now a major public health issue. One-third of the population suffers from deficiency even in sunny Australia, with substantially greater rates seen in migrant communities. In the United States, spending on supplements has increased tenfold while the prevalence of vitamin D deficiency has increased (Spedding, 2014). So, this study showed vitamin D is closely related to causing depression. However, depressive illnesses frequently coexist and have a significant negative influence on public health. In other words, it is crucial to consider depression as a significant risk factor for a wide range of age-related illnesses. These correlations may be partially explained by the dysregulation of physiological stress systems, including inflammation, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, including metabolic dysregulation. Also, it has been discovered that those with depressive illnesses are more susceptible to accelerated biological ageing. Depression has been discovered to have a connection to biological ageing that is more advanced, which is consistent with its detrimental effects on a variety of ageing-related somatic illnesses. For instance, this is demonstrated by the fact that depressives have shorter telomeres length than

healthy controls. A very well-studied indicator of cellular age, telomere length (TL), incorporates the cumulative lifetime cost of genetic factor as well as environmental factors that are based on chronological age and predicts a number of disorders associated with ageing as well as early mortality (Marwood et al., 2018). As a result, in this review paper, the possible connection between vitamin D, depression, and the aging process is currently being investigated.

1.2 Objectives of the Study

The following are the study's objectives:

- To provide an insight on the role of vitamin D in the development of depression
- To discuss the relationship between depression and ageing
- To establish a relationship among vitamin D, depression and ageing

1.3 Rationale of the Study

Depression is a widespread and impairing mental condition that affects people of all ages, genders, and races and vitamin D, a fat-soluble vitamin, is widely believed to help in the body's absorption as well as retention of both phosphorus and calcium. A few recent studies have revealed a hypothesis that emotional and depressive conditions are somewhat linked to vitamin D shortage or insufficiency because the brain has vitamin D receptors. Along with that, a deficiency of vitamin D has been linked to various neurological disorders and several psychological illnesses. To have a thorough grasp of the connection between vitamin D and depression, this review presents different study results on patients. Nowadays, ageing is also related to depression. Depression and ageing share the same characteristics in that both cause the entire brain to show dynamic changes indicative of atrophy. Major Depressive Disorder (MDD) and one of the hallmarks of ageing-telomere length shortening have an inverse cross-sectional correlation, which suggests that the depressed have biological ageing that is more advanced than the usual process. Since depression can accelerate the process of ageing and a shortage of vitamin D is thought to play a significant influence in the development of depression, this study aims to establish a relationship among these three aspects, which might aid the patients in overcoming depression and hence, slow down the process of ageing.

Chapter 2 Methodology

The information for this study was collected from various primary and secondary authentic databases like PubMed, ScienceDirect, Google Scholar, and Research Gate and from some reliable websites. Most of the information was taken from recent articles, research papers, review papers, etc. At the very beginning of executing this review paper, an outline was prepared in a systematic manner. In order to search information relevant to the topic, key phrases used include causes of depression, vitamin D deficiency consequences, hallmarks of ageing, the association between vitamin D and depression, an association between vitamin D and ageing, etc. Duplication articles were removed before adding references and finalizing the paper. After going through more than 80 articles and 50 relevant papers, information was chosen to write up the whole review paper.

Chapter 3 Depression

3.1 What is Depression?

Depression is a complex condition with many different manifestations, including physical complaints such as weariness and aches, negative effects on mental health, and loss of interest (Högberg et al., 2012). It is a widespread mental illness that jeopardizes both the physical and psychological well-being of people everywhere. It has been said that depression is the "common cold" of psychiatry. Depression is undoubtedly widespread and also is typically found in moderate versions, which helps to expand the analogy a little. However, in its most extreme symptoms, it is the primary worry that may consume a sick individual to the extent of suicide. A formal major depressive episode can occur alongside practically any other mental or medical diagnosis. Patients who see their doctors with depressive symptoms and other indicators of human sorrow sometimes have both major and moderate depression, dysthymia, and depressive symptoms (Goodwin, 2006). In younger children, depression symptoms may include melancholy, irritability, clinginess, worry, aches and pains, unwillingness to attend school, or having underweight. Grief, mood swings, feelings of negativity and worthlessness, frustration, poor accomplishment, or poor academic performance, experiencing confusion and being extremely sensitive, using alcohol, having to eat or sleep excessively, self-harming behaviors decreasing enthusiasm for everyday activities, and reduction of socialization are all symptoms of depression in teenagers. Depression is not a normal part of becoming older, and it should never be treated lightly. Regrettably, depression typically goes unnoticed and untreated in older folks, who may be hesitant to seek treatment. Major depressive disorder (MDD) was identified as the primary source of global illness burden in middle- and high-income nations in 2008, being the most significant antecedent to suicide (Zhang et al., 2022).

3.2 Types of Depression

3.2.1 Bipolar Disorder Depression

Bipolar depression is indeed a complex combination of serious and persistent disorders which include bipolar I disorder, which is distinguished by the occurrence of one or more symptomatic, manic episode, with bipolar II disorder, distinguished by the presence of a symptomatic, psychotic

condition as well as an episode of severe depression. Extra deaths from cardiovascular illnesses and suicide account for the majority of the mortality differential between bipolar disorder groups with the rest of the population. Bipolar disorder is passed down through generations (approximately 70% of the time). Bipolar illness shares genetic risk factors with several other mental and physiological diseases. Bipolar I is more genetically linked to schizophrenia than bipolar II is to severe depressive disease. Depression may be more prominent in bipolar 2 patients. Over a 13-year naturalistic follow-up period, in one study, bipolar II individuals had a 37:1 ratio of depressed to hypomanic week. Longer-term research addressing the safety and effectiveness of antidepressants, as either monotherapy for bipolar II patients or just in conjunction with psychiatric drugs in bipolar I and perhaps II patients, is unsurprisingly scarce. In bipolar patients, practice guidelines generally advocate relatively short-term antidepressant medication (Gitlin, 2018).

3.2.2 Melancholic Depression

Because of its clinical characteristics, Previously, melancholic depression was regarded to be a serious form of major depressive illness. Despite the common features of MDD, such as decreased responsiveness of mood and affect, a pervasive and severe depressive state exists, melancholic depressive disorders are marked by widespread anhedonia, feelings of inadequacy, psychomotor interruption, such as retardation as well as spontaneous restlessness, cognitive impairment in working memory, and vegetative dysfunction, such as sleep disruption, insatiable hunger, and weight loss, and these features are highly consistent. But it is uncertain whether melancholy depression is a separate mental condition or a possible subtype of MDD. Cognitive healing takes longer in melancholic MDD patients than in non-melancholic persons. Also, patients with melancholy MDD had a higher risk of recurrence than those with non-melancholic MDD. As a result, the diagnosis of melancholy MDD has a higher predictive validity for therapy and prognosis (Yan et al., 2021).

3.2.3 Persistent Depressive Disorder (PDD)

Chronic depression may begin sooner (before the age of 21) and have worse results than non-chronic depression, including single or repeated severe depression with complete inter-episode healing. Assessments of the features, prevalence, and burden of disease as opposed to non-depression, on the other hand, are complicated by two considerations: most knowledge is derived

from clinical specimens and the prevalence rate differs. There was no widely accepted description of chronic depression until the American Psychiatric Association decided in 2013 to include a new major depression subtype, which is persistent depressive disorder (PDD), added in the recently released edition of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-IV). PDD is described as depression lasting at least for two years. Hence, the PDD subtype combines the DSM-IV diagnoses of major depressive disorder (MDD) with dysthymic disorder (DD). The newest PDD diagnostic category sometimes does not take into account significant lifetime evidence. As a result, we know relatively little about persistent depression over a lifetime. Furthermore, the DSM-5 PDD diagnosis is mostly based on clinical data. very little is known about chronic depression across the lifespan, and the notion of PDD has been questioned because its reliability has never been rigorously tested (Nübel et al., 2020).

3.2.4 Disruptive Mood Dysregulation Disorder (DMDD)

There has been substantial controversy in recent times regarding the most suitable diagnostic classification for children who demonstrate emotional distress in the manner of irritation and extreme temper tantrums. This is what has most recently manifested in the inclusion of a new diagnosis, Disruptive Mood Dysregulation Disorder (DMDD), in the DSM 5. The goal for integrating this new disease was to reduce the number of diagnoses such as PDD that were previously given to these children; nevertheless, there is concern that it will have only broad consequences rather than simplifying them. According to a current epidemiologic investigation, DMDD cannot be separated from oppositional defiant disorder (ODD) which is known as behavior disorder based solely on symptoms like consistent patterns of impatience, bickering, and disrespect toward parents as well as other power figures. Disruptive Mood Dysregulation Disorder is such a condition that would benefit greatly from a Research Domain Criteria (RDoC) viewpoint. DMDD is a contentious diagnosis characterized by mood disturbances and disruptive conduct. This new illness developed from anxiety that children's pathological restlessness and rage were not being adequately identified and treated. More particular, despite the chronic vs episodic character of their symptoms and evidence for separate etiology, many of these children were being labeled with bipolar disorder. The problem is that similar symptoms are exhibited in a wide range of mood and disruptive behavior problems; the invention of DMDD was meant to address this issue.

Nonetheless, research has called into doubt the validity of DMDD as a distinct diagnosis (Meyers et al., 2017).

3.2.5 Premenstrual Dysphoric Disorder (PMDD)

The condition known as premenstrual syndrome is defined as reoccurring modest physical and psychological signs that emerge throughout the luteal stage of menstruation and then vanish. It affects 20–32% of premenopausal women. Women suffering from premenstrual dysphoric disorder have affective as well as somatic disorders which potentially cause impairment in social and occupational settings. The illness affects 3–8% of premenopausal women. Increased susceptibility to typical circulating levels of estrogen as well as progesterone, elevated aldosterone, and plasma renin activity, including neurotransmitter disorders, especially serotonin, are proposed etiologies. The Daily Record of Severity of Issues is one tool that allows women to self-reporting the presence and severity of premenstrual symptoms that match the DSM-IV criteria for the premenstrual dysphoric disorder. The goal of premenstrual syndrome and premenstrual dysphoric disorder treatment is to relieve symptoms. There is insufficient evidence to support the administration of calcium, vitamin D, and vitamin B6 supplementation, as well as therapy for cognitive behavior. As a first-line treatment serotonergic antidepressants such as citalopram, escitalopram, fluoxetine, sertraline, venlafaxine, and others are being used (Hofmeister & Bodden, 2016).

3.2.6 Depressive Disorder Due to Other Medical Conditions

Cancer can increase the risk of depression in many kinds of ways. Initially, reactions resulting from an extreme diagnosis, along with the subsequent deterioration of health history, maybe a contributing factor to depression; Furthermore, treatment with immune system response modifiers and chemotherapy regimens, in addition to metabolic and endocrine abnormalities, persistent discomfort, and extensive invasive surgery, may also be contributors. The percentage of significant depression among cancer patients is believed to be over 15% in oncological as well as hematological settings, with similar dimensions in primary healthcare settings. When other depressive diagnoses, such as dysthymia and mild depression, are included, the prevalence rate rises to 20% in oncological, especially hematological settings and up to 25% in palliative care configurations (Ostuzzi et al., 2018).

3.3 Causes of Depression

3.3.1 Age

According to a meta-analysis, depressive disorders are considered to be the greatest frequent mental diseases in the elderly, with an average prevalence of 7.2% (95% CI 4.4-10.6%) for severe depression and 17.1% (9.7-26.1%) for depressive disorders exceeding clinically significant depression criteria among people aged 75 and more. Furthermore, in an age-stratified, random sample of 3142 men and women aged 65 to 84 years in Western countries, the European MentDis_ ICF65+ study observed 12-month estimations of prevalence of 11.6% (9.5-13.6%) for major depressive episodes and 2.5% (1.3-3.7%) for any bipolar disorder in an age-stratified (Hussenoeder et al., 2021).

3.3.2 Gender

Depression is a common mental condition that has major consequences for both physical and mental health. Women are more likely than males to suffer from depression. Depression vulnerability is influenced by a variety of inherited, epigenetic, environmental, and endocrine risk factors. The gender gap in depression incidence begins in childhood and continues into old life, however, the adult gender gap is less significant than it is in young adulthood. Men and women with depression have different symptom characteristics. Increased appetite, hypersomnia, physical discomfort, and other indications are more common in women. Depression has emerged swiftly in both men and women throughout adolescence, especially in females. Similarly, the heritability of depression increased from childhood by way of adolescence (Zhao et al., 2020).

3.3.3 Lifestyle

- **Role of sleep, diet, exercise, and smoking-**

Mental diseases afflict over 30% of people throughout their lives, accounting for 32% of all years lived with disability. Given the limited number of psychiatric treatments available, a considerable segment of the worldwide population lacks access to standard mental health care, particularly in many low- and middle-income nations. A large body of cross-sectional evidence indicates that a variety of psychotic disorders, such as schizophrenia, bipolar disorder, as well as depression, are

associated with adverse health behaviors, when compared to healthy counterparts, they have comparatively poor routines for eating and sleeping, inadequate physical exercise, and higher rates of tobacco smoking. Furthermore, new data from large-scale research show that the links between a number of these risk factors for lifestyle diseases and mental disease exist in low- and middle-income nations (Firth et al., 2020).

- **Effect of working people and university students-**

Keeping a sitting-centric lifestyle in adulthood can result in health hazards. Current research indicates that people who spend more time sitting have a higher risk of obesity and depression. Some researchers have looked at sedentary lifestyles, activity levels, and problems with physical health, but few have looked at sedentary conduct as well as mental health. Among so many studies, an Australian study discovered that sedentary activity was unrelated to psychological health and quality of life. Another Australian study found that office workers who sat for more than 6 hours a day had much higher psychological distress compared to those who did not. Also, in an investigation involving university students in Spain, individuals who sat for more than 42 hours per week had a 31% greater risk of mental illnesses than individuals who did not. Since 2003, South Korea has ranked #1 across Organization for Economic Cooperation and Development (OECD) countries in terms of suicide fatality (28.7 per 100,000 people). Suicide accounts for 45.5% of deaths among those aged 20 to 29. Furthermore, stress, worry, and depression among university students were discovered to have an immediate influence on the number of suicides. It is critical to maintain and develop a healthy lifestyle while at university and to sustain such practices into adulthood (Lee & Kim, 2019).

3.3.4 Genetics

As the field of developmental behavioral genetics grew in popularity, more researchers began to focus on the significance of genetic variables in the incidence of gender inequalities in depression. Quantitative genetics and molecular genetics are two approaches used in behavioral genetics research. The genetic variables influencing depression symptoms differ depending on the participant's developmental stage or age: Persons in early childhood had a larger heritability in depressive mood than those in mid-adolescence, according to both self-reports and parent reports. Genetic variables grow more relevant from childhood to adolescence. Various genes may have a

gender-specific effect on depression. 5HT2A ("5-HT" = 5-hydroxytryptamine), also known as serotonin), TPH (Tryptophan hydroxylase) could represent a hazardous gene for depression in women, while COMT (catechol-O-methyltransferase protein) may be more important in men (Zhao et al., 2020).

3.4 Assessment Methods for Depression

The steps to assess depression or depressive symptoms include:

Interview

In the latest research, worldwide sites that provided information on CM (child maltreatment) to the ENIGMA MDD Workgroup consented to participate in the Childhood Adversity Subgroup. Most of the research has been done using the SCID-1 along with CIDI, and sometimes another type of structured interview. They reviewed data from 3872 people in total: 1284 individuals with a history of MDD and 2588 HC. All participating venues received local permission from institutional boards and ethical committees. Furthermore, the Otto von Guericke University Magdeburg's medical faculty's ethical board accepted this meta-analysis (Tozzi et al., 2020).

Questionnaire

The Hamilton Depression Questionnaire (HDRS-17) was employed at some sites to determine the level of severity of depression symptoms now of scanning, while the Beck Depression Inventory (BDI-II) and in a few cases Inventory of Depressive Symptomatology-Self Report (IDS-SR) also implemented at others (Tozzi et al., 2020).

Image Processing and Analysis

MRI brain scan was performed locally through each site in all participants, and the scans were processed using the fully automated and proven categorization software Free Surfer (version 5.0 or higher). Every sample's image capture parameter and program specifications are given. For segmentation accuracy deep brain structure volumes were extracted and visually evaluated. Depending on the Desikan-Killiany atlas and left and right hemisphere assessments, parcellations for cortical thickness as well as the surface area of about 68 areas (34 right and 34 left) were

generated and carefully examined for accuracy using a protocol aimed at facilitating harmonized imaging techniques throughout multiple sites (Tozzi et al., 2020).

The Statistical Framework of Mega-analysis

To evaluate the clinical severity of depression from the scans, ANOVA or Kruskal-Wallis tests were used. The 2 tests were used to examine differences in male and female frequency distributions. Finally, using the surface area of each location as the predictor variables, researchers created generalized estimating equation (GEE) models. Their models responded on a linear scale. Regardless of diagnosis, all subjects were included. They incorporated the between-subjects factors diagnosis (factor: 1 = patients, 0 = HC), sex (factor: 0 = men, 1 = females), and hemisphere in all models (left, right) (Tozzi et al., 2020).

Investigation of Clinical Confound

A subset of MDD samples (N= 966) contained more thorough clinical data, allowing them to investigate possible additional confounding factors. As a result, they examined clinical severity (continuous: BDI(Beck depression inventory) total score, because HAM-D (Hamilton Rating Scale for Depression) was only offered to a select group that took part, recurrence (factor: 0 = first episode, 1 = recurrent episode), present antidepressant utilization (factor: 0 = no, 1 = yes). Because clinical remission statistics were not supplied by all sites, we characterized it as the current BDI⩽12 for this study (Tozzi et al., 2020).

3.5 Management of Depression

3.5.1 Psychotherapy

Over the last few decades, many approaches to psychotherapy for depression have been created and tested in primary care. The definition of psychotherapy as "the informed and intentional application of clinical methods and interpersonal stances obtained from accepted psychological principles for the intention of helping individuals to reconfigure their behavior patterns, cognitions, emotional responses, and/or other personal attributes in directions deemed desirable by the participants. As most primary settings care behavioral activation therapy (BAT), cognitive behavior therapy (CBT), problem-solving therapy, interpersonal psychotherapy (IPT), and non-

directive counseling have been studied. According to a significant body of data, psychotherapies are effective in the treatment of depression. In randomized trials, therapies are often compared to standard treatment, a period of inactivity, a pill placebo, or another control setting. When compared to the control conditions, the impacts are mild to significant. There is little evidence that the results of different forms of therapy differ considerably. Direct comparison studies, in addition to network meta-analyses, show that the outcomes of all major modalities of therapy are equivalent. Even though the number of investigations was limited, one meta-analysis examining the distinct impacts of psychotherapies operated in primary care appears to support this having found no significant differences among therapies. Some distinction was discovered between IPT and internet-based CBT, however, this was predicated on a limited amount of research and mostly indirect proof. Psychotherapies can indeed be provided in primary care by general practitioners (GPs),social workers, trained nurses, or clinical psychologists. There has been little investigation into who administers the treatment (Marwood et al., 2018).

3.5.2 Medications

Antidepressants are the most commonly given psychotropic medicines in persons suffering from depression. Numerous unique antidepressants are obtainable, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and relatively new agents which including agomelatine, mirtazapine, reboxetine, as well as bupropion. It has been repeatedly demonstrated that SSRIs do not prove more efficacious than TCAs (Ostuzzi et al., 2018).

3.5.3 Complementary Medicine

Natural medicines have seen a considerable increase in popularity in the past few decades to treat a variety of diseases, including both anxiety and depression. These things are considered as better alternatives to medicine, with a lower risk of adverse effects or symptoms associated with withdrawal. Several people prefer herbs over conventional pharmaceuticals for symptom treatment because they have limited efficacy and negative effects.

In most investigations, lavender, saffron, and passionflower had benefits equivalent to standard anxiolytics and antidepressants. Also intriguing are black cohosh, chamomile, as well as a chaste

berry. All researchers studied anxiety or depression symptoms, occasionally serving as primary outcomes. Overall, 45% of trials found beneficial results with fewer side effects when compared to traditional drugs. When compared to standard therapies, black cohosh, chaste berry, chamomile, passionflower, lavender, and saffron appear to be useful in relieving anxiety or depression with good risk-benefit profiles (Yeung et al., 2018).

3.5.4 Brain Stimulation Therapy

Despite considerable issues, deep brain stimulation (DBS) is frequently used to treat Parkinson's disease (PD).It is also used, albeit off-label, in the therapy of major depressive disorder. DBS is an experimental treatment for treatment-resistant depression (TRD). There is preliminary evidence that the subgenual anterior cingulate cortex, the lateral habenula, the ventral capsule/ventral striatum, the nucleus accumbens, the medial forebrain bundle, the inferior thalamic peduncle, and the bed nucleus of the stria terminals have been used as a DBS target in treating severe depression, demonstrating the safety and efficacy of electric stimulation (sACC), and the mechanism of DBS appears (Drobisz & Damborská, 2019).

Chapter 4 Vitamin D

4.1 Vitamin D

- **Function**

Vitamin D is a lipid-soluble steroid hormone having various important molecular and cellular functions. Apart from bone mineralization, vitamin D is indeed engaged in cell differentiation and renewal of numerous organs; it is said to impact glucose homeostasis and effectively play a role in the preservation of the musculoskeletal system's physiological activities. Sufficient vitamin D consumption has been demonstrated to reduce the risk of various skeletal and non-skeletal illnesses. It has various functions in the body, including cell development regulation, neuromuscular and immunological function, and inflammation control.

Two major forms of vitamin D-
-Vitamin D_2 is derived from plant sources. It is commonly used in fortified food products and vegetarian supplements.
-Vitamin D_3 is the form of vitamin D synthesized in the skin when exposed to sunlight. Animal-based food sources, like fatty fish (e.g., salmon, mackerel), fortified dairy products, and egg yolks also consist of vitamin D_3

However, to perform biological functions vitamin D must be transformed from its storage or inactive state (25[OH]D) to an activated state ($1,25[OH]_2D$) (Uwitonze & Razzaque, 2018). Vitamin D is still being explored for its function in autoimmune disorders, multiple sclerosis, infections, cardiometabolic disease, respiratory disease, cancer, and fracture risk (Pfotenhauer & Shubrook, 2017).

- **Sources of vitamin D**

When exposed to sunshine, the skin produces vitamin D_3 (cholecalciferol). As a result, vitamin D is not a true vitamin. Individuals that get plenty of sunlight don't need to take any supplements. Because most people do not get enough vitamin D from their diets, safe sunshine exposure or the ingestion of vitamin D-fortified foods is recommended. Vitamin D, whether D_3 (animal source) or D_2 (plant source), has no biological function. Rather, it must be further metabolized in the liver and

kidneys to produce the physiologically active form 1,25-dihydroxy vitamin D (1,25[OH]$_2$D), also known as calcitriol (Uwitonze & Razzaque, 2018).

As a result, there are two sources of vitamin D:

· **Food and sun exposure**

The impact of direct sunlight on the skin surface, which contains UVB radiation with wavelengths 290-315 nm, results in vitamin D production.

· **Naturally occurring dietary sources of vitamin D**

There are a few food supplements like many but not all fish (salmon, tuna, sardines, swordfish) (5-25 g/100 g), Reindeer lichen (87 g/100 g), mushrooms (21.1-58.7 g/100 g), and fish liver oils (250 g/100 g) are strong sources of vitamin D (D denotes D_2 and D_3). Additional food sources include cheese, eggs (1.3-2.9 g/100 g), dark chocolate (4 g/100 g), and fortified foods like yogurt, milk, orange juice, fat spreads, plant-based beverages, and breakfast grains are all good sources of vitamin D. In the United States, fortified foods contain synthetic vitamin D_2 (ergocalciferol) generated from the irradiation of ergosterol found in mold ergot, plants, or plankton. Because an adequate intake of vitamin D (15 g/day as advised by the European Food Safety Authority) can be challenging to achieve just via diet, vitamin D supplements for digestion are usually prescribed (Pfotenhauer & Shubrook, 2017).

4.2 Synthesis of Vitamin D

The amount of vitamin D generated in the skin is influenced by the incidence angle of the sun, which is determined by season, latitude, period, and time of day (Alonso et al., 2019). Both vitamin D3 and D2 are inactive within the body. They must be converted to their effective metabolite via enzymatic means. First, it is 25-hydroxylated inside the liver, producing 25 (OH)D (calcidiol), the most prevalent circulating version of vitamin D with a half-life of approximately two to three weeks. Afterward, it proceeds 1-alpha-hydroxylation via the kidneys to create its most active form, 1,25(OH)2D (calcitriol), that has a half-life of approximately four to six hours. PTH, in addition to other mediators that include hypophosphatemia and growth hormone, activates this pathway. Non-renal locations where 1-alpha-hydroxylation occurs include alveolar macrophages,

osteoblasts, lymph nodes, placenta, colon, breasts, and keratinocytes, implying a potential autocrine-paracrine involvement for $1,25(OH)_2D$. In other words, vitamin D_3 and D_2 can enter the bloodstream and attach to the vitamin D binding protein (VDBP). Vitamin D is primarily delivered to the liver and hydroxylated at C-25 by the cytochrome P450 enzyme (CYP2R). Cytochrome P450 [5(OH)D-1hydroxylase; CYP27B1] performs a second hydroxylation at the C1 site in the kidneys. The finest vitamin D nutritional status indicator, 25-hydroxyvitamin D ($25(OH)D_2$ or $25(OH)D_3$), is then created. Following that, $25(OH)D_3$ is converted to 1, 25-dihydroxy vitamin D ($1, 25(OH)_2D_3$), the highest active form of vitamin D (Geng et al., 2019a). A flowchart illustrating synthesis of vitamin D is given in Figure 1.

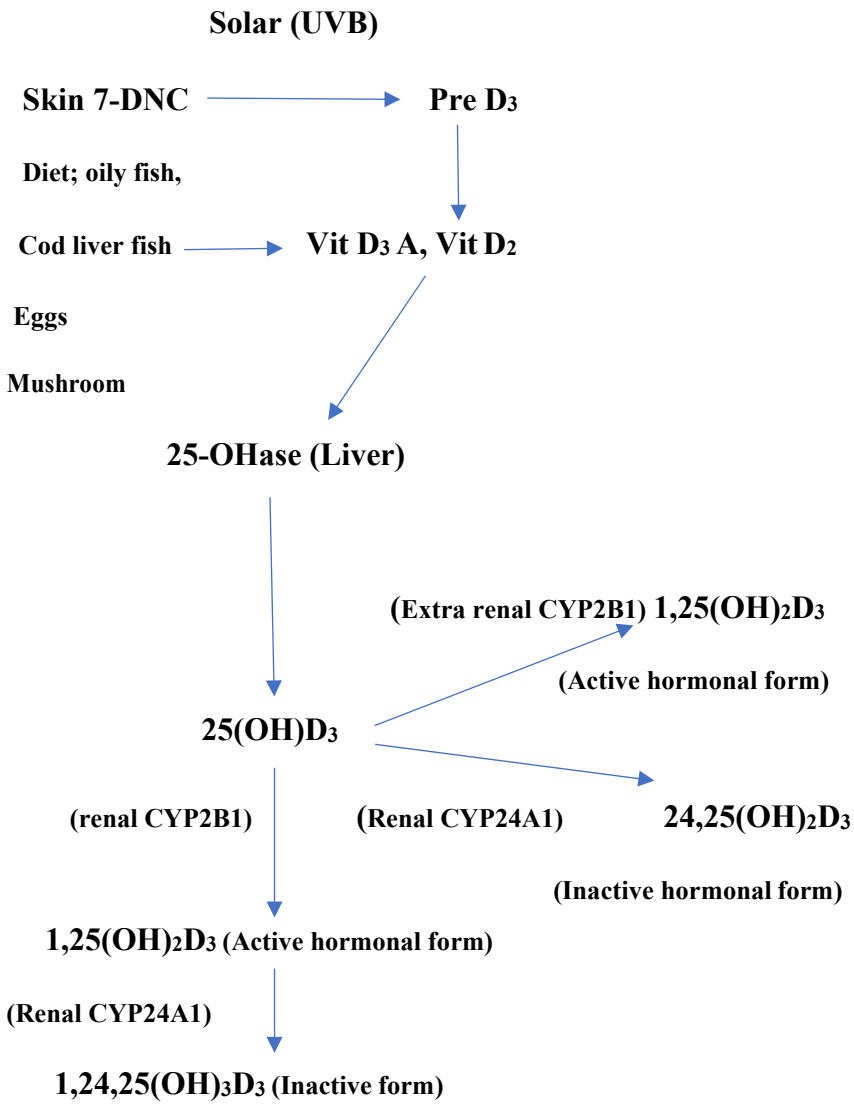

Figure 1: Process of vitamin D synthesis

4.3 Risk Factors of Vitamin D Deficiency

The risk factors for hypovitaminosis include the winter season mostly occurs in October to March mainly in the northern hemisphere, causes skin pigmentation, applying suntan lotions as well as oils, skin thinning (aging gives rise to significantly reduced D_3 production), reduced outdoor exposure (immobilized and institutionalized patients), malnutrition, covered up clothing, kidney and liver disease, malabsorption, and the consumption of antiepileptic drugs (secondary hyperparathyroidism with any of these drugs) (Chu et al., 2010). Vitamin D insufficiency can be caused by a variety of factors. Decreased skin synthesis may happen because of aging when 7-dehydrocholesterol levels in the skin fall. Melanin absorbs greater UVB radiation, resulting in darker skin pigmentation. The application of sunscreen absorbs UVB (Ultraviolet B) radiation. The quantity of sunlight entering the skin is affected by the latitude, season, and time of day. the sun's zenith angle help to determine the quantity of solar UVB photons that reach the Earth. Reduced 25 (OH) D synthesis can occur as a result of liver failure and prolonged renal sickness, whereas increased 25 (OH) D urine loss can occur as a result of nephritic syndrome. (Parker & Brotchie, 2011).

4.4 Diagnosis of Vitamin D Deficiency

There is an overwhelming consensus that serum 25OHD is the most reliable marker of vitamin D status considering several studies in older people have demonstrated its relationship with biochemical parameters such as PTH and clinical observations such as bone mineral density (BMD) and fracture risk. These links, however, are not observed in all studies and vary between races, cultures, and ages. Additionally, technical difficulties in 25OHD measurement must be considered for value interpretation because 25OHD assays have a differing affinity for vitamin D_2 and D_3.

Some potential indicators of the level of vitamin D, such as the vitamin D metabolite ratio 25OHD/24,25$(OH)_2$D, and the free as well as bioavailable forms of 25(OH)D, have been investigated over the past years, however, there is currently insufficient evidence to apply their use in daily practice. The European Food Safety Authority (EFSA) recently released a technical Report on Nutrient Dietary Reference Values. These values represent the amount of nutrients that must

be ingested daily to improve health in a healthy individual. According to the review, the existing data on non-musculoskeletal health outcomes is insufficient to justify setting Vitamin D Dietary Reference Levels. (Alonso et al., 2019).

Chapter 5 Relationship between Vitamin D and Depression

5.1 Mechanism of Action

Despite the fact that the underlying pathophysiology of vitamin D in depression is unclear, the following are the main depressive mechanisms hypothesized to be connected with vitamin D.

i. Vitamin D and Neurotrophic Hypothesis

Immunohistochemical studies found vitamin D receptors (VDRs) in the brain's central nervous system (CNS), providing the first substantial evidence that vitamin D may have a role in brain function. The VDR with the vitamin D activation enzyme 1-alpha-hydroxylase may be found in a variety of brain cells, including neurons in the glial and amygdala cells in the hypothalamus. 1,25(OH)2D3 may pass the blood-brain barrier to bind to VDR in particular parts of the brain, particularly the hippocampus, raising the hypothesis that vitamin D plays a role in cognitive function, in either a direct or indirect manner. In the meantime, the hippocampal structure may affect memory, the emotional function of other parts of the brain, as well as the hippocampus alongside other limbic structure atrophy.

Vitamin D has been found to be an efficient regulator of neurotrophic agent synthesis, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophic factor (NT)-3. Neurotrophic factors are required for neuron formation, survival, and migration. They do so by interacting through their cognate tropomyosin-related kinase (Trk) receptors, including BDNF/TrkB, NGF/TrkA, NT-3/TrkC, and the corresponding neurotrophic receptor p75 (p75NTR). A large body of investigation has shown that 1,25(OH)2D may raise the expression of BDNF, NGF, and NT-3 while decreasing the expression of NT-4 in brain astrocytes, adding to the evidence that vitamin D may influence neuron survival and differentiation. As a result, vitamin D modulates the production of neurotrophic agents, the abnormal function of which is linked to a range of psychiatric diseases (Geng et al., 2019b).

ii. Vitamin D and Monoamine Neurotransmission Hypothesis

According to the conventional monoamine neurotransmission hypothesis, monoamine insufficiency may be an underlying factor of depression; more specifically, depression is linked to serotonin (5-HT), dopamine (DA), and norepinephrine (NE). Typical antidepressant medicines, including tricyclics, work by blocking the 5-HT and NE transporters. 5-HT, a monoamine neurotransmitter, is generated from the amino acid tryptophan, and speculations about its function in the pathophysiology of depression date back to the 1960s. A small amount of research suggests that 5-HT plays a significant role in brain activities associated with mood regulation. Yet a deficiency of vitamin D may impair 5-HT production, resulting in aberrant brain and serotonergic neuron activation.

The VDR accumulates in neurons that produce dopamine located in the hippocampus, substantia nigra, and prefrontal cortex of humans and rats, all of which have a role in depression. In vitamin D insufficiency, VDR development in the substantia nigra may delay DA cell development and produce DA-mediated behavioral deficits. It also implies that a lack of vitamin D may disrupt dopaminergic neurodevelopment, resulting in major implications for the progression of depression. As a result, vitamin D may be able to play a vital role in depression by affecting the levels of 5-HT, DA, and NE, in either a direct or indirect manner (Geng et al., 2019b).

iii. Serum Vitamin D Concentrations and Depression

Levels of serum vitamin D have gained considerable attention; in the mid-to-late 1980s, generally, serum 25(OH)D concentrations were commonly used for measuring the level of vitamin D since circulating 25(OH)D was regarded to be the most accurate indicator of vitamin D nutritional status. Increasing research has linked 25(OH)D levels to a variety of disorders, including cardiovascular disease, diabetes, cancer, obesity, as well as asthma. It ought to be mentioned that vitamin D has the potential to influence the development of neurotrophic factors including interleukins. As a result, the significance of vitamin D in both the prevention and treatment of depression is getting greater attention. Several research has yet to reach a general conclusion on whether decreased levels of serum 25(OH)D have a strong connection with depression.

Recent investigations, on the other hand, have failed to show a link between levels of 25(OH)D in the blood and depression in female subjects or in elderly participants. Because of a limited number of participants and socio-demographic factors such as genetics, sex differences, body mass index, family affluence, residence, parental levels of education, diet, subjective academic achievement, drinking, along with smoking, there are discrepancies when validating previous findings associations. Decreased serum vitamin D levels, without a doubt, show a non-significant yet elevated risk for depressive disorders (OR 1.31, 95% CI 1.00-1.71). As a result, the most essential thing to do right now is to summarize and compile the best available information to understand the mechanism of vitamin D in both the prevention and treatment of depression (Geng et al., 2019b).

5.2 Methodology on Assessing the Relation between Vitamin D and Depression

A study conducted by Menon et al. used the following assessment methodology to determine the association between low vitamin D and depression (Menon et al., 2020).

Participants

A combined total of 200 participants were chosen from different regions of Peshawar, Pakistan, at Khyber Teaching Hospital Peshawar, Cantonment Board Hospital Peshawar, and Lady Reading Hospital Peshawar, which includes 100 people in good health and 100 depressed individuals (outpatients). The identified participants, aged 20 and under to 60 and over, were adequately screened using the Beck's Depression Inventory (BDI) scale. Everyone who took part in the study gave their consent for the study. The ethics committee at the Shaheed Benazir Bhutto Women's University in Peshawar, Khyber Pakhtunkhwa, Pakistan, accepted the study protocol. The study mentioned in the paper completely fulfills the ACS ethical Guidelines for animal studies (Khan et al., 2022).

Collection of blood sample

Participants' blood samples (3 mL) were taken, labeled, and kept in vials at 4°C. For 10 minutes, the tubes were spun in a centrifuge at 5000 rpm. The vitamin D level in the blood serum was determined (Khan et al., 2022).

Determination of vitamin D level

The patients' emotions and histories were used to differentiate between depressed and normal volunteers. The level of depression was examined after the preliminary identification of depressed subjects. The serum was isolated for vitamin D measurement. Abbott's Architect Plus monitors serum vitamin D levels. The data was automatically collected and analyzed on the CI 4100 instrument, where the vitamin D level was calculated and reported in ng/mL (Khan et al., 2022).

Depression level estimation

The BDI scale established was utilized to determine the level of depression in all 100 depressed patients found. The BDI survey has 21 sets of statements that are required to estimate a subject's depression degree. As a result, in a typical experimental approach, the most relevant statement with all three groups was ringed by obtaining the history of the depressed participants. The completed questionnaire was graded (khan et al., 2022).

Result

The vitamin D levels of 100 healthy and 100 depressed people were examined to assess the relationship between vitamin D levels and depression. They were grouped into three groups based on their age, namely Group-I, which included subjects under the age of 20, Group-II, which included subjects between the ages of 21 and 60, and Group III, which included subjects over the age of 61, and observations were taken.

The vitamin D and depression profiles of 41 male depression characteristics were evaluated. According to the data, the mean SEM of age is 38.87 ± 2.089, and the CV is 34.41%. The mean SEM of the vitamin D level provided is 24.17 ± 1.32, with a 34.96% CV. The mean SEM of depression level on the BDI scale is 25.8 ± 1.49, with a 37.17% CV. This also shows the age, vitamin D, and depression profiles of all 59 female depression patients. The data gathered revealed that the mean SEM of age was 45.5 ± 1.87 and the CV was 31.56%. The mean SEM of vitamin D level provided is 23.36 ± 1.81 and 59.76% CV. The mean SEM of depression indicated is 28.06 ± 0.95, while the standard deviation is 25.86% CV (Khan et al., 2022).

5.3 Different Study Results on Patients

Epidemiologic studies of vitamin D levels and depression

- **Cross-sectional studies**

Over the years, at least five cross-sectional epidemiological studies on various foreign community groups have been conducted. The Centre for Epidemiologic Studies-Depression (CES-D) scale was used to assess the degree of depression and severity. The researchers discovered that 25 (OH) D levels were reduced by 14% in 169 people diagnosed with moderate depression and 14% reduced in the 26 people identified with serious depression, indicating that lower 25 (OH) D levels corresponded with higher levels of depression severity. After controlling for gender, age, smoking skill, BMI level, and the number of health issues, the last connection remained significant. The Nutrition and Health of the Ageing Population in China (NHAPC) project conducted community-centered cross-sectional research among middle-aged with elderly Chinese to examine the relationship between depression as well as blood 25 hydroxyvitamin D (25(OH) D) levels in the population as whole. Volunteers were 3262 people in the community aged 50 to 70. The 20-item Centre for Epidemiologic Studies-Depression (CES-D) Scale, which has been validated in Chinese populations for major depression, was used to assess depressed symptoms. The study's researchers concluded that there was no evidence relating depressed symptoms to 25(OH) D levels. A lack of vitamin D was linked to a significantly higher risk of developing a mood illness (odds ratio = 11.7) and found that, whereas lower 25 (OH) D levels were linked with depression caseness or intensity in numerous samples, there were also several instances of non-significant studies in populations. The study's researchers decided that there was no evidence relating depressed symptoms to 25(OH) D levels (Parker & Brotchie, 2011).

- **Clinical studies**

There was accumulating evidence that vitamin D may play a role in the link between seasonal mood changes and photoperiod shifts. Serum 25(OH) D levels were tested in a clinical cohort of 17 adults with both bipolar and unipolar depression throughout the summer months because that time levels are higher. Only three participants had readings within their laboratory's normal range (60-160 nm l), and the average level in the blood was 47.0 nm l (males had a level that was lower than females). A short double-blind intervention research in which eight individuals with SAD

were randomly assigned to either 100,000 IU of vitamin D daily or phototherapy and found that people who got vitamin D supplementation benefited on depression measures. The rise in 25(OH) D levels was substantially associated with mood improvement (Parker & Brotchie, 2011).

- **Longitudinal studies**

Researchers conducted a 6-year prospective analysis on 954 people aged 65 and up to explore the relationship between low vitamin D levels at baseline and future (incident) depression. For those with 25(OH)D3 50 nm (or higher) levels relative to the ones with high levels at baseline, individuals with low levels at baseline had significantly greater depression measurement scores at 3- and 6-year follow-ups. Women's anticipated strength in relationships was more distinct than men. This study added to the evidence of a causal link between low vitamin D and depression by controlling for a variety of possible confounding factors and investigating the relationship between the variables of interest and prospectively symptoms associated with high levels of 25(OH) D (Parker & Brotchie, 2011).

- **Cross-sectional studies of mood disorder, seasonality, and vitamin D**

Recently released Japanese community-based observational research involved in the investigation of 527 people aged 21 to 67 years old found no link between 25(OH) D3 and depressive symptoms (13), while they did discover an increasing tendency for vitamin D for having a protective impact on symptoms of depression. A recent regional community study involving 2070 older people mostly 65 years or older in England discovered that deficiency of vitamin D was associated with late-life depression at northern latitudes, though higher levels of depression were observed only in individuals with a particularly serious lack of vitamin D state, alongside no statistically significant improvements in connections with milder relative deficiency. These findings are consistent with those of an Amsterdam investigation, which found lower 25 (OH) D levels to be related to both moderate and minor depression, when compared to the summer season, late autumn (their sun-deprived season) is preferable (Parker & Brotchie, 2011).

- **RCTs and open studies of SAD symptoms and vitamin D**

A randomized controlled trial (RCT) with a one-year follow-up included a large number of obese or overweight people, including men and women who are between ages 21 to 70. Depression

ratings on the Beck Depression Inventory (BDI) were higher in individuals with low levels of 25 (OH) D at baseline, albeit this did not correlate with depression severity. Participants randomly allocated to receive either 40 000 or 20 000 IU of vitamin D each week showed an improvement in symptoms of depression over a twelve-month period but the placebo had no effect. In that a lack of vitamin D precedes and increases the danger of depression, various reasons have been proposed, including impaired growth factor for nerve synthesis and involvement of a range of possible neurotransmitter targets. Vitamin D accessibility has an opportunity to change brain endocrine function related to psychiatric as well as neuropsychiatric diseases, particularly in certain mental disorders having seasonal patterns and where significant variations in the sun (UVB) exposure could result in vitamin D shortage (Parker & Brotchie, 2011).

Various studies on patients have been conducted to determine the relationship between Vitamin D and depression as shown in Table 1.

Table 1: Different studies conducted on patients to determine the relationship between Vitamin D and depression.

Organization	Population	No of population	Pre-existing	Assessment	Vit D level	Dose of Vit D	Types of study	Reference
Nutrition and Health of Ageing Population in China (NHAPC) project	middle-aged and elderly Chinese	3262 residents aged between 50–70 year	major depression	20-item Centre for Epidemiologic Studies-Depression (CES-D) Scale	<50 nm (insuffient)	800 IU/d	populatio n-based cross-sectional study	(Parker & Brotchie, 2011a).
United Kingdom epidemiologic al study	European	3369 with a mean age of 60 years	seasonal affective disorder (SAD)	Epidemiologic Studies-Depression (CES-D) Scale	<50 nm (insufficien t)	800 IU/d	cross-sectional study	(Parker & Brotchie, 2011a).
Community-based observational study in Japan	Japanese	527 subjects aged between 21 and 67 years	Deficiency in relation between25(OH) D3 and symptoms of depression	Beck Depression Inventory (BDI) scale	<50 nm (insufficien t)	600 and 4000 IU daily(in winter)	Cross-sectional studies	(Parker & Brotchie, 2011a).
Cantonment Board Hospital Peshawar, Khyber Teach-ing Hospital Peshawar, and Lady Reading Hospital Peshawar.	Pakistani	200 subjects,	100 healthy individuals and 100 depressed individuals	Beck Depression Inventory (BDI) scale	<50 nm(or<20 ng⁄ml)(depressed individual)	1 to 70y 600IU/d And 71y above 800IU/d	Question aries	(Khan et al., 2022)

Amsterdam Public Health Research Institute, Amsterdam UMC,	European	155 participants aged 60–80 y	clinically relevant depressive symptoms	randomized placebo-controlled trial	15–50/70 nmol/L	1200IU/d	RCT study	(De Koning et al., 2019)
6-year prospective study was undertaken by Milaneschi et al		954 adults aged 65 years or older		Epidemiologic Studies-Depression (CES-D) Scale	<50 nm (or<20 ng⁄ml)	800IU/d	Longitudinal studies	(Parker & Brotchie, 2011a).

Chapter 6 Correlation of Depression and Ageing

6.1 Aging

Aging is defined by an ongoing degradation of physiological integrity, which leads to reduced function and a higher probability of death. This degradation is the leading cause of major medical conditions such as diabetes, cancer, neurological illness, and cardiovascular disease. In present generations, aging research has made tremendous advances, most notably the discovery that the aging process is regulated, at least in part, by genetic routes and metabolic mechanisms preserved throughout evolution. This review identifies nine potential hallmarks (Figure 2) that indicate common characteristics of aging in various taxa, with a focus on mammalian aging (López-Otín et al., 2013).

Hallmarks of aging are-

1. Altered intercellular communication.
2. Stem cell exhaustion
3. Cellular senescence
4. Mitochondrial dysfunction
5. Genomic instability
6. Telomere attrition
7. Epigenetic alteration
8. Loss of proteostasis
9. Deregulated nutrient sensing. (López-Otín et al., 2013).

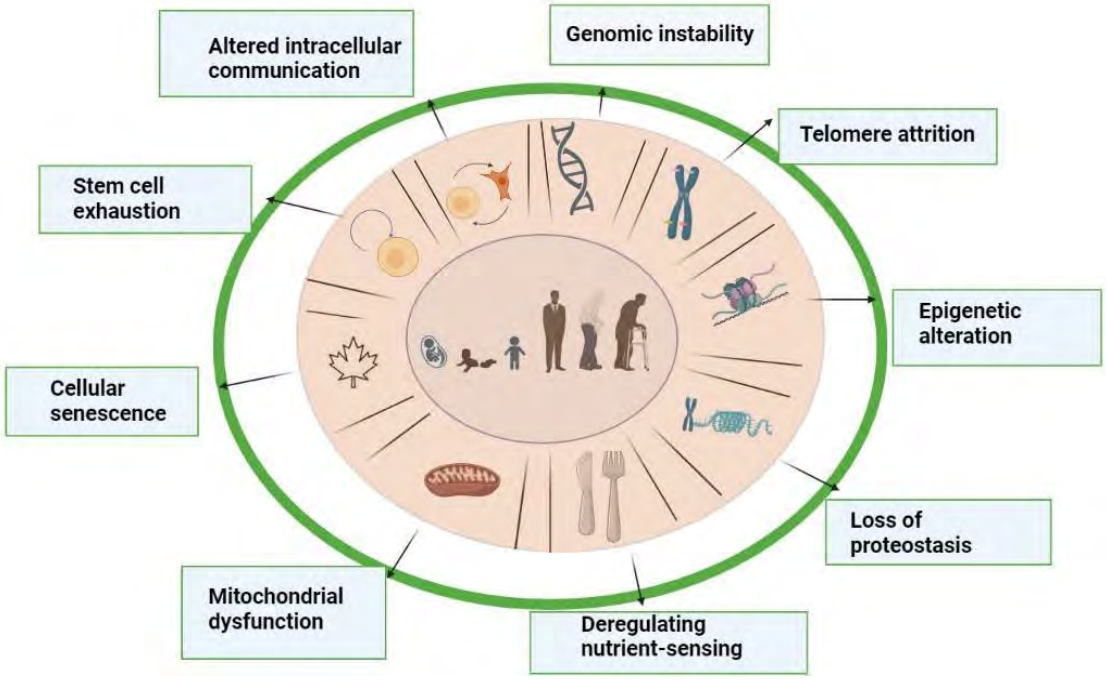

Figure 2: Hallmark of aging (Adapted from López-Otín et al., 2013)

6.2 Relationship between Depression and Aging

Major depressive disorder (MDD) is being postulated to be a "disease of premature aging" that includes certain indicators of cellular aging and a variety of different age-related disorders. Telomere length (TL) shortening has emerged as a surrogate for accelerated cellular aging throughout the last decade (Manoliu et al., 2018). Along with that, aging can cause depression, which is caused in part by physical health issues and incapacity. Because of teleological evolutionary explanations or mundane lifestyle implications, aging may be affected by both positive and negative state of mind and response to stress. On the negative side, people who suffer from mood and stress disorders have a considerably shorter life expectancy (Hammen, 2005). Depression has been linked to an increase in biological aging, as seen by shortened telomere length, quicker brain aging, as well as greater epigenetic aging. Being overweight, frailty, diabetes, dementia, cognitive decline, and mortality are all increased by depression.

Many progressive, fatal illnesses are characterized by depression. A growing amount of research connects depression to cardiac, cerebrovascular, and peripheral artery disorders. Depressed people

have a 45% higher risk of stroke and a 25% greater risk of stroke-related death than non-depressed people. These findings suggest that depression predisposes people to a variety of medical disorders and these illnesses can raise the likelihood of late-life depression (LLD) as well (Alexopoulos, 2019).

According to one study, people with any medical condition were twice as probable to be depressed as patients lacking a medical diagnosis. Depression rates in neurological conditions have long been acknowledged as greater than expected, and significant argument has ensued regarding the probable biological versus reactive elements of this depression. For example, lifetime depression prevalence rates among Parkinson's disease (PD) patients exceed 70%, and depression in PD is related to greater cognitive impairment, faster progression of the disease, and increased disability. Individuals with Huntington's disease (HD) were also asked about the existence, frequency, and severity of depression symptoms in order to better describe depressed mood throughout the illness course in HD. One-half said they were looking for medical care for depression, and more than 10% said they had attempted suicide at least once (Dean & Keshavan, 2017).

The phenomenon, if depression leads to accelerated cellular aging or advanced biological aging leads to depression due to increased risk of developing several illnesses or both are existing, is still unequivocal due to limited studies. However, there seems to be a link among telomere shortening, aging and depression as recent evidence suggests that telomere length is shorter in people with MDD compared to non-depressed people and telomere attrition is also one of the hallmarks of aging (Manoliu et al., 2018).

6.2.1 Different Study Results on Patients

i. Potential mediators of shorter telomeres in MDD patients

- **Inflammation and oxidative/nitrosative stress**

Inflammatory along with oxidative stress have been associated to telomere shortening and have been connected to MDD. On the level of cells, oxidative stress and inflammation have been demonstrated to produce senescent characteristics in mature neurons. Oxidative as well as nitrosative stress, in general, refers to cells' inability to remove nitrosative (RNS) or reactive oxidative (ROS) substances via antioxidative mechanisms Aerobic cells create ROS/RNS as a consequence of various metabolism processes; in specific, mitochondria transform 1% to 5% of

the oxygen ingested to ROS/RNS. When the amount of ROS/RNS produced exceeds the cellular capacity of existing antioxidative systems, ROS/RNS can cause oxidative damage to a variety of components, including DNA. Notably, cellular anti-oxidative capability declines with age, leading to a higher rate of oxidative damage throughout the aging process in addition to an increased risk of severe somatic illnesses. Telomeric DNA is especially vulnerable to oxidative stress, and healing of oxidative damage is very ineffective in telomeres, implying that LTL could be an alternative for a lifetime measure of accumulated oxidative damage. In those suffering from MDD, researchers measured interleukin (IL)-6 as a peripheral indicator of inflammation and F2-isoprostane/vitamin C ratio as a peripheral indicator of cellular oxidative stress and discovered that IL-6 had a strong correlation with shorter telomeres those are patients with MDD, while F2-isoprostane/vitamin C proportion had been related with shorter telomeres with MDD along with healthy control subjects in individuals, providing additional proof that inflammatory mechanisms might explain reported findings (Manoliu et al., 2018).

- **Dysregulation of the HPA axis**

Based on multiple studies, the connection between psychosocial stress and telomeres are significant and are frequently seen at the beginning of life. Shortening of telomeres has been linked to damaging childhood interactions and/or circumstances, including mental, physical, and emotional sexual abuse and/or emotional/physical neglect, socioeconomic issues which include economic hardship, parental being unemployed, parental mental and physical illnesses, familial conflict, harassment, particular illness, parental death, parental separation or divorce, including being subjected to domestic violence. Considering its importance for comprehending stress response, various studies have concentrated on the hypothalamic-pituitary-adrenal (HPA) axis to study how psychosocial stress or depression can manifest as physiological malfunction and clinical dysfunction. The HPA axis is the primary neuroendocrine response to stress mechanism that works to adjust the organism to both intrinsic and external stimuli, maintaining homeostasis and health. Psychosocial pressure or depression activates the HPA axis, resulting in the release of cortisol, which is able to be utilized as one indicator of stress reactivity. *In vitro* investigations have revealed that administering hydrocortisone to lymphocytes reduces telomerase activity. Given this finding, as well as the constant link between stress and telomere shortening, it is reasonable to speculate that HPA axis dysfunction may also be linked to telomere shortening.

6.3 Establishing a Relationship between Vitamin D, Depression, and Aging

Vitamin D levels have been found to be low in people who suffer from mood disorders, and its mechanism of action is thought to be linked to depression. Even after just a few minutes of being exposed to sunshine, vitamin D production in fair skin is extremely rapid and considerable. The main and most important source of circulating vitamin D is accidental sun exposure. When exposed to sunshine in the summertime, the skin may produce 20,000 IU of sunlight-sensitive vitamin D in less than 30 minutes. A major population research study carried out in the United States in 89 distinct geographical locations found that the frequency of depression is higher in those with low vitamin D levels than in those with normal vitamin D levels. It has been discovered that vitamin D affects the gene expression of one of the key enzymes, tyrosine hydroxylase, which plays a role in the synthesis of dopamine and norepinephrine. These neurotransmitters are well-known for their function in depression and mood disorders. Vitamin D is required for the maintenance of physiological processes such as calcium homeostasis, membrane permeability, axonal transmission, and neurotransmission. Vitamin D triggers receptors in the limbic system, cerebral cortex, and cerebellum, which are areas of the brain involved in the control of behavior and feelings. It also increases the release of neurotrophin, which is vital in maintaining the balance of neuronal growth (khan et al., 2022).

Aging, which we characterize generally as the time-dependent functional decrease that impacts most living beings, has piqued people's interest and sparked their creativity across history. Aging is currently being studied scientifically in light of our growing understanding of the cellular and molecular underpinnings of life and illness. Many scientists have been trying to determine and classify the cellular and molecular markers of aging. They offer nine possible hallmarks that are widely thought to have contributed to the process of aging and, when combined, determine the aging phenotype. Among the nine distinguishing features is telomere length (TL) shortening has emerged as a surrogate for the aging of cells over the last decade (López-Otín et al., 2013). Recent evidence suggests that TL may be shorter in people with MDD, however, the results are still equivocal. Clinical studies have attempted to elucidate a possible link between shorter telomeres and MDD throughout the last decade. Short telomeres among individuals have been linked to a variety of medical disorders, including heart disease, diabetes, and cancer. Several studies have

linked shorter leukocyte telomere length (LTL) to premature death and a decrease in years of active living (Manoliu et al., 2018).

People with vitamin D deficiency have been found to have increased risk of developing depression. Depressed patients show accelerated cellular aging due to telomere shortening. Therefore, a correlation between vitamin D, depression, and aging can be established from the limited studies conducted.

Chapter 7 Research Gaps and Future Directions

While the review paper on establishing a relationship among vitamin D, depression, and ageing provides valuable insights, there may be certain research gaps that could be addressed in future studies. Some potential research gaps include:

- Some intervention studies have found that Vitamin D supplementation may be beneficial for depressive symptoms and ageing-related outcomes, but because little research has been conducted, no solid advice can be given by the data set. There is still a need for well-designed randomized controlled trials (RCTs) with larger sample sizes (Parker & Brotchie, 2011b).
- Determining the optimal vitamin D levels for mental well-being and healthy ageing is another research gap.
- While some potential mechanisms linking vitamin D, depression, and ageing have been proposed, there is still a need for further research to elucidate the underlying biological processes. Investigating the specific pathways through which vitamin D influences mental health and ageing-related processes can help identify therapeutic targets and develop more effective interventions.
- The impact of vitamin D on depression and ageing may vary across different populations, including diverse ethnic groups, individuals with specific medical conditions, and those with varying levels of sun exposure. Conducting studies that focus on specific populations can help identify potential variations in the relationship and inform targeted interventions.
- In a comprehensive examination of trial data, Rejnmark et al. reviewed the available evidence on the extraskeletal impact of vitamin D and highlighted that most of the research was conducted on people with adequate 25(OH)D levels, which could clarify the null findings of many trials.

Chapter 8 Conclusion

This review paper explores the current fundamental mechanisms of depression that involve vitamin D. Even though the data on the connection between vitamin D as well as depression is contradictory, lower levels of 25(OH)D in the blood have been linked to an increased risk of depression, and symptoms of depression in people with exceptionally low levels of vitamin D could be alleviated by vitamin D supplements. Monitoring serum 25(OH)D concentrations can also assist us understand about our health state while offering unique insights regarding depression in some situations. In addition, this review structured the ideas into it and expect that efficient and secure protocols to cope with depression will be established (Geng et al., 2019b). The potential relationship between vitamin D and accelerated ageing is also an area of ongoing research. While the exact mechanisms are not fully understood, several factors suggest a possible link between vitamin D and the ageing process, such as preservation of telomere length, cognitive functions, muscle functions, inflammation and oxidative stress. Moreover, depression and ageing are two interconnected aspects that can significantly impact an individual's well-being. Depression is not uncommon among older adults, and its prevalence tends to increase with age. Maintaining adequate vitamin D levels may play a role in the prevention of depression and accelerated ageing. However, further research, including well-designed clinical trials, is needed to establish definitive causality and optimal strategies for vitamin D supplementation.

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