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DEPRESSION OR DEMENTIA IS RELATED MORE TO ALZHEIMER'S DISEASE (AD)

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Abstract:

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive and behavioral impairment that significantly interferes with social and occupational functioning. Depression and dementia are common in the elderly and frequently occur together. The timing of depression may be important in defining the nature of the association. Depression in early life doubles dementia risk, while depression in later life is more probable to be prodromal to dementia. The risk to develop AD is higher in mild cognitive impairment (MCI) than in depressed elderly. Depression in MCI hastens conversion to Alzheimer's disease. In cognitively normal elders, the presence of depression increases the risk of MCI. From theories that explain the association between depression and AD are vascular depression theory, increased cortisone level, a higher burden of ab plaques, chronic inflammatory processes, and accelerated cellular aging. The current evidence is insufficient to assess the benefits vs. harms of screening for cognitive impairment in the elderly. If dementia is suspected, physicians can use brief screening. If the results are abnormal, further evaluation is warranted. Finally, MCI was the first predictive condition that increased the risk to develop AD. Depression is an additional risk factor for conversion to AD in MCI.

Keywords: *Alzheimer's disease, Dementia, Mild Cognitive Impairment, Depression.*

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INTRODUCTION:

Dementia is a significant and costly health condition that affects 5 million adults and is considered the fifth leading cause of death among Americans older than 65 years. The prevalence of dementia will likely increase in the future because the number of people older than 65 years is expected to double by 2060 [1].

The overall prevalence of dementia is approximately 5%, reaching 37% in persons older than 90 years. The lifetime risk of dementia is approximately 17%, with the incidence doubling each decade after 60 years of age [2]. The median survival time after diagnosis of dementia is 4.5 years, but this differs based on age at diagnosis, ranging from 10.7 years for patients diagnosed in their 60s to 3.8 years for patients diagnosed in their 90s [2].

Alzheimer's disease accounts for 60% to 80% of all dementia cases [3]. Every 65 seconds someone in the United States develops Alzheimer's disease. By 2050, seven million people aged 85 and older are expected to have Alzheimer's dementia, (about 51 % of all people 65 and older with AD [2].

One-third of people living with dementia also experience depression. Treating symptoms of depression may be a protective factor and reduce cognitive decline in dementia [4]. Late-life depression is usually associated with Cognitive decline, making it difficult to be differentiated from dementia. Neither the symptoms of dementia nor those of depression are normal for elders. They are symptoms that significantly affect the quality of life for both those who are affected and their caregivers [5]. Depression may be a risk factor, a prodrome, or a consequence of dementia [6]. A recent study revealed that 22.85% of patients with MCI convert to dementia within 3 years of follow-up [l]. On the other hand, the risk to develop AD, within four years, was 68.33% for MCI and 49.57% for depression. In AD patients 5.60% deteriorated without depression, and 72.20% deteriorated with depression after 4 years of follow-up [7]. This article will review the relationship between depression and dementia with AD, theories of association between depression and dementia, appropriate screening tools for early detection AD, and the role of family physicians in dementia care.

METHODS:

A review was conducted up to August 2022 using the databases PubMed and Google Scholar. The research terms included Alzheimer's disease, Dementia, Mild Cognitive Impairment, and depression. The exclusion criteria include papers published before 2000 and papers that don't address the association of Depression or Dementia with Alzheimer's disease (AD). All duplicates were erased and screened by the title, abstract, and full text. In recent decades, several epidemiological studies and reviews have investigated the risk factors for depression and dementia. However, little literature review specifically summarizes all evidence about Depression or Dementia is related more to Alzheimer's disease (AD). The aim is to provide an updated comprehensive review of studies conducted on Depression or Dementia related more to Alzheimer's disease (AD).

Epidemiology of Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive and behavioral impairment that significantly interferes with social and occupational functioning. It is an incurable disease with a long preclinical period, insidious onset, and a slowly progressive course. According to a 2017 Alzheimer's Association report, AD affects an estimated 6.08 million people in the United States, and approximately 200,000 people younger than 65 years with AD constitute the younger-onset US population with AD [2,7].

A larger number of individuals have decreased cognitive function (mild cognitive impairment), this condition frequently converted to dementia, thereby increasing the number of affected persons. By the year 2050, AD is predicted to affect 13.8 million persons in the United States [2].

The characteristic symptoms of dementia are difficulties with memory, language, learning, problem-solving, and other cognitive skills that affect a person's ability to perform everyday activities and impair quality of life. These difficulties occur because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged. In Alzheimer's disease, neurons in other parts of the brain are ultimately damaged or destroyed as well, including those that enable a person to perform basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require higher care. Alzheimer's disease is finally fatal [8].

One in three seniors dies with Alzheimer's or another dementia. In the United States, AD is a leading cause of death. While deaths from other major causes have been decreasing, deaths from of AD have been rising. AD was estimated as the sixth leading cause of death in 2017 [9]. Moreover, AD as an underlying

cause of death is frequently underreported [10-14]. About 18.4 billion hours of care, valued at over $232 billion, are provided by family and other unpaid caregivers.

Risk factors for Alzheimer's disease

The cause of AD is unknown. Several investigators now consider that environmental and genetic risk factors trigger a pathophysiologic cascade that, over decades, leads to Alzheimer's pathology and dementia [15].

Older age remains the chief risk factor for dementia. Other strong risk factors include a family history of dementia; previous personal history of cardiovascular disease, cerebrovascular disease, diabetes, or midlife obesity; use of anticholinergic medications; apolipoprotein E4 genotype; and lower education level [16-19].

Other potential risk factors with weak evidence include smoking, atrial fibrillation (independent of stroke risk), substance abuse, some medications such as alcohol, proton pump inhibitors, and benzodiazepines, and head trauma [20-23].

Hypertension is a well-known risk factor for late-life dementia, of which AD is the most common type. A brain autopsy study evaluating the link between hypertension and AD found that patients the used of beta-blockers had fewer Alzheimer's-type brain lesions on autopsy compared to patients taking no drug therapy or those taking other medications [24].

In addition, recent epidemiologic studies have suggested some possible risk factors such as previous history of depression [25]. Other studies have suggested protective factors such as a high level of education [13], and prolonged use of nonsteroidal anti-inflammatory drugs [26].

Depression as a risk for dementia

Co-occurring dementia and depression, particularly in older adults, presents distinctive challenges for healthcare practitioners. Symptoms of dementia, such as impairment in memory, language, thinking, behavior, and the ability to perform everyday activities [27] can appear similar to symptoms of depression, which may include depressed mood, psychomotor retardation, poor concentration, loss of interest and loss of energy [28]. Approximately one-third (32%) of people living with dementia are also likely to experience depression [29].

In the 2017 Draft Global Action Plan on the Public Health Response to Dementia, the World Health Organization (WHO) identified that preventing and managing depression may be a protective factor and reduce the risk of cognitive decline in dementia [26].

Late-life depression is frequently associated with cognitive impairment. Depressive symptoms are usually associated with or even precede dementia syndrome. Moreover, depressive disorders increase the risk of persistence for mild cognitive impairment and dementia. It was found that Depression occurring for the first time in late life may indicate a prodromal stage of dementia. On the other hand, Treating depression slow the progression of mild cognitive impairment to dementia [30].

Depression has been identified as a risk factor for AD and other dementias. There is a 50% increase in AD and dementia in those who were depressed at baseline. During a 17-year follow-up period, a total of 21.6% of elders who were depressed at baseline developed dementia, as compared with 16.6% of those who were not depressed [13].

Depressive symptoms occur frequently in 30%–50% of AD dementia while the occurrence of full criteria of major depression accounts for 10% of AD [31,32].

Depression may occur acutely as a major or clinical episode, as a seasonal affective disorder, or as an adjustment to a new situation. It can also occur chronically as dysthymia or persistent depression that extends over several years. Most frequently, it presents as a late-life depression possibly associated with inflammation, hormonal, and immune issues impacting the frontostriatal circuits and or the hippocampus. Cognitive decline is usually associated with late-life depression, making it difficult to be differentiated from dementia. Neither the symptoms of dementia nor symptoms of depression are normal as people age. They are symptoms that significantly decrease the quality of life for both those who are afflicted and their caregivers [5].

Risk factors for late-life depression include female sex, social isolation, being a widow, being divorced or separated, having lower socioeconomic status, having comorbid general medical conditions, uncontrolled pain, insomnia, and cognitive and functional impairments [31]. For noninstitutionalized older patients, rates of depression are supposed to be similar to those of the general adult population; however, as many as 50% of nursing home residents may be depressed [1]. Depression is a major risk factor for

suicide, especially in older men, with suicide rates in elders increasing with age. A study showed that men older than 75 years have the highest annual incidence rate of suicide at 39 deaths per 100,000 men, compared with four deaths per 100,000 women older than 75 years [33].

Depression or dementia is related more to Alzheimer's disease (AD)

Alzheimer's disease may follow depression or dementia. Kida et al. found that the risk of developing dementia, in particular AD, for the amnestic mild cognitive impairment (aMCI) was significantly higher than that for the non-amnestic mild cognitive impairment (naMCI) [33]. In the (aMCI), the presence of depressive symptoms increased the risk of developing AD, on the other hand, depressive symptoms in the naMCI group did not. Moreover, in the cognitively normal group, the presence of depressive symptoms increased the risk of aMCI but not naMCI or AD [34].

A recent study showed that 22.85% of patients with MCI convert to dementia after 3 years of follow-up [35]

Another study showed that the risk to develop AD, within 4 years of follow-up, was 68.33% for aMCI and 49.57% for late-life depression (LLD). In AD patients 5.60% deteriorated without depression, and 72.20% deteriorated with depression after 4 years of follow-up. It was found that (aMCI) was the first predictive condition that increased the risk to develop AD while Depression is a potentially preventable condition across the lifespan and is considered a modifiable risk factor [7].

On the other hand, Sacuiu et al. investigated the association of chronic depressive symptomatology (chrDS) with the occurrence of cortical atrophy rates and subsequent conversion to Alzheimer's dementia (AD) over 3 years in mild cognitive impairment (MCI). They found that 42.7% of patients with chrDS developed AD. Participants with chrDS had a 60% shorter conversion time to AD than those without depressive chrDS [36].

The risk of developing dementia later in life increases twofold in the presence of a positive history of depression at a younger age. In the presence of recurrent depressive disorders, a consistent rise in the risk of dementia can be observed with an estimated 14% increase with each episode [37]. A recent study suggested that chronic depression during life may be etiologically associated with an increased risk for developing dementia, particularly vascular dementia, whereas depression occurring for the first time in late life may reflect a prodromal stage of dementia, in particular AD [38].

Kuan et al., reported that in major depressive disorders (MDD) patients support the hypothesis that a higher amyloid burden is associated with poorer memory performance. they observed a high prevalence of MCI among elderly depressed patients, and depressed patients with MCI exhibited heterogeneously elevated ^{18}F-florbetapir retention as compared with depressed patients without MCI. The higher amyloid burden in the aMCI patients suggests that these patients may also be more likely to develop Alzheimer's disease than other patients diagnosed with major depression [39].
Elvira Lara et al., revealed that Depression significantly increases the risk for MCI. Targeting depression among those at risk for dementia may help delay or even prevent the onset of dementia. Depression at baseline predicted the onset of MCI at follow-up after controlling for socio-demographics, cognitive functioning, and other physical health conditions (OR = 2.79; 95% CI = 1.70, 4.59). The effect of baseline depression on incident MCI subtypes was as follows: amnestic MCI, OR = 3.81 (95% CI = 1.96, 7.43); non-amnestic MCI, OR = 2.03 (95% CI = 0.98, 4.21) [40].

Depression is frequently associated with dementia

Depression and dementia are common in older people and frequently occur together. Large-scale community surveys in the United States using structured interviews found that the point prevalence of the major depressive disorder in community-living adults aged 65 and older is 3.0-4.3%.' Depression affects up to 20% of patients with Alzheimer's disease and up to 45% of patients with vascular dementia [41]. The comorbidity of depression and dementia is more than that simply expected by chance, implying that they are related [42]. Their interrelationship, however, is not well understood. Depression can be an independent risk factor, a prodromal symptom or a consequence of dementia [43]. Current research suggests that the timing of depression may be important in defining the nature of the association. Depression with onset before the age of 60 has been related to a two-fold increase in dementia risk [44]. Recent meta-analyses, which included other types of dementia confirm these findings [45,46]. Rather than a risk factor, depression with onset in later life is more probable to be either prodromal to dementia [46] or a condition that unmasks pre-existing cognitive impairment by compromising cognitive reserve and thus shortening the latent period between the occurrence of dementia-

related pathology and the onset of clinical symptoms [48].

Brommelholf and his colleagues reported that depression diagnosis within ten years of dementia onset was usually associated with a four-fold increase in the likelihood of having dementia, while depression onset occurring more than ten years prior to dementia onset has no effect [49].

Depression can be seen as a psychological response to getting a diagnosis of dementia. Studies that found high rates of anxiety and depression, particularly early in the course of dementia support this explanation [13].

It is unclear whether shared vascular risk factors themselves cause structural and functional brain changes that increase the risk of depression and dementia, or whether increased vascular risk factors for depression start a pathway that leads to an elevated risk of dementia. Research to date prefers a bidirectional relationship, especially as vascular risk factors may lead to the development of other organic brain changes including hippocampal atrophy, increased deposition of amyloid-beta plaques, and inflammatory changes [50,51].

Association between depression and dementia

Currently, several mechanisms have been suggested to explain the association between depression and dementia [30]. First, there is significant evidence indicating that vascular disease is the primary link between depression and dementia, which is proved by the "vascular depression hypothesis" [52,53]. This pathophysiological theory states that cerebrovascular disease is a risk factor or a trigger for depressive syndromes in the elderly [54]. Vascular changes in the frontostriatal brain regions have been linked to both depression and cognitive impairment [55-57].

In addition, increased cortisone levels, a biochemical alteration frequently observed usually in depressive disorders [58], lead to worsening hippocampal atrophy associated with cognitive deficits [54,59]. Notably, atrophy of the hippocampus is a well-characterized brain alteration detected both in AD [60] and in patients with depression [61,62].

The presence of accumulating brain amyloid beta (Ab) plaques represents the main pathologic hallmark of AD. It is well-known that both Ab peptides and hyperphosphorylated tau proteins accumulate significantly in AD brains, leading to the formation of neurotic plaques and neurofibrillary tangles, respectively [63,64]. Interestingly, evidence indicates that depression might lead to an increased disequilibrium in terms of Ab production and/or clearance. This outcome is mediated by the depression-related stress response and the resulting increased cortisone level, as well as the direct impact on Ab processing, probably due to changes at the level of the serotonergic system [65–69]. Notably, depressed AD patients have a higher burden of Ab plaques and neurofibrillary tangles in the hippocampus than AD patients without depression [70–73].

During the last decade, chronic inflammatory processes have been also involved in both depression and dementia [74–76]. Moreover, chronic brain inflammatory state, inducing cellular imbalance resulting in increased concentrations of brain cytokines detected in depression and dementia, that result in a reduced modulation of anti-inflammatory and immunosuppressive mechanisms, increased acute-phase, and pro-inflammatory regionally spreading alterations in the central nervous system, and, ultimately, in a non-linear progressive fashion inducing neural network imbalance, decompensation and breakdown, cognitive deficits, and subsequent dementia [77]. Moreover, pro-inflammatory cytokines overexpression is supposed to affect with serotonin metabolism, thereby decreasing both synaptic plasticity and hippocampal neurogenesis [67,74].

Another mechanism that may link depression with dementia is represented by decreased levels of circulating neurotrophic factors, mainly the brain-derived neurotrophic factor (BDNF). BDNF modulates neuronal structure and function and plays an essential role in synapse development and plasticity [78]. Reduced plasma BDNF levels have been observed both in animal models of depression [79] as well as in patients with depression [80,81] and AD [82,83].

Recent data have shown that depressed patients face accelerated cellular aging. In particular, those with the most severe and chronic major depressive disorder exhibited the shortest telomere length, and participants with remitted major depressive disorders had shorter telomere lengths than controls [84].

A more comprehensive systems-based neurobiological approach—larger genetic and epigenetic studies, analyses of gene and biomarker expression patterns, as well as innovative multimodal structural, functional, and metabolic neuroimaging—is needed to shed more light on the pathophysiology of

late-life depression. To this aim, much can be learned both conceptually and methodologically from recent discoveries in the field of AD [85–87].

Early detection of Alzheimer's dementia

Alzheimer's disease is frequently misdiagnosed and there is a delay in diagnosis. The U.S. Preventive Services Task Force and the American Academy of Family Physicians have settled that current evidence is insufficient to assess the benefits versus harms of screening for cognitive impairment in older adults. If dementia is highly suspected, physicians can use brief screening tests such as Mini-Cog or General Practitioner Assessment of Cognition as recommended by Alzheimer's Association. If the results of initial brief tests are abnormal, further evaluation is necessary using more in-depth screening tools such as the Montreal Cognitive Assessment, Saint Louis University Mental Status Examination, or Mini-Mental State Examination. Diagnostic testing and secondary evaluation usually include screening for depression using the geriatric depression scale or a more valid screening tool such as the Cornell scale for depression in dementia, appropriate laboratory studies to exclude other conditions that cause cognitive impairment, and magnetic resonance imaging of the brain, should be performed when cognitive impairment is confirmed. Routine cerebrospinal fluid testing and genetic testing for the apolipoprotein E4 allele are not recommended [1].

Brief screening tests are useful to quickly assess the need for further evaluation. In 2013, the Alzheimer's Association recommended three screening tests that could be completed within the time frame of a Medicare wellness visit: Mini-Cog, Memory Impairment Screen, and General Practitioner Assessment of Cognition [88]. These tools are simple and require less than five minutes to complete, can be administered by non-physician personnel as they don't need training, and are validated in the primary care office setting. Subsequently, a systematic review called into question the sensitivity of the Memory Impairment Screen within well-designed studies [89]. The care setting, has little to no education bias, and availability in multiple languages [89]. The patient screen consists of recall, time orientation, clock drawing, and information components. The patient screen takes less than four minutes to complete, and the informant portion takes less than two minutes. The General Practitioner Assessment of Cognition has a sensitivity of 85% and specificity of 86% [89].

Patients who screen positive for cognitive impairment on brief screening tests should be evaluated further to quantify the degree of impairment [90]. A variety of tools are available for this purpose. The Mini-Mental State Examination (MMSE) is the most used cognitive evaluation tool [91]. The test has a sensitivity of 89% and a specificity of 81% for detecting dementia [89]. A nomogram establishes cutoff scores depending on the patient's age and education. The Montreal Cognitive Assessment and Saint Louis University Mental Status Examination are alternatives to the MMSE. Both are 30-point cognitive tests that take approximately 10 minutes to administer. The Montreal Cognitive Assessment is designed for persons scoring above 24 on the MMSE and has excellent accuracy in detecting mild neurocognitive disorders [91].

The Diagnostic and Statistical Manual of Mental Disorders, 5th ed., updated the diagnostic criteria for dementia and mild cognitive impairment, introducing the terms major and minor neurocognitive disorders instead of dementia [92]. The major neurocognitive disorder requires the demonstration of significant cognitive decline in at least one of the following cognitive domains: complex attention, executive function, language, learning and memory, perceptual-motor, or social cognition. This decline must be based on both subjective and objective findings, and interfere with instrumental activities of daily living. The minor neurocognitive disorder requires only modest cognitive decline that does not interfere with instrumental activities of daily living.

In order to meet the DSM5 criteria for AD, the individual must meet the criteria for major or mild neurocognitive disorder and there should be insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired). The individual must also meet criteria for either probable or possible AD as defined in the DSM5[13,92].

Role of the family physician in Alzheimer's Dementia

As family physicians are generally patients' first point of contact with the health system, they are ideally placed to provide care for individuals living with dementia from the early stage to the end stage of the disease. They have a full and long-term understanding of the medical, social, and psychological situations of these patients and their families [93]. Timely detection, diagnosis, and care of those living with dementia are predominantly the responsibility of primary health care practitioners, particularly family physicians [94]. Family physicians should be involved in developing, leading, and implementing models of

care for elders, including those living with dementia and Alzheimer's disease [95-97].

Family physicians influence dementia rates by working with patients to diminish risk factors. [98,99]. Dementia is not an inevitable consequence of aging. Reducing smoking and alcohol consumption, managing hypertension, diabetes, obesity, depression, and hearing loss, maintaining social engagement, and increasing exercise are all factors that contribute to the prevention or delay of dementia [98,99].

The key role of the family physician in dementia care includes prevention, the diagnostic process (including timely diagnosis, dementia staging, and differentiating dementia subtypes), communication of the diagnosis to the patient, and post-diagnosis management through person-centered, integrated care and family physicians should provide caregiver support and dementia training [93].

CONCLUSIONS:

- Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive and behavioral impairment that significantly interferes with social and occupational functioning accounting for two-thirds of dementia cases.
- Depressive symptoms are often associated with or even precede a dementia syndrome and may be reactive to dementia diagnosis
- Various theories have been suggested to explicate the association between depression and dementia
- Mild cognitive impairment (MCI) was the first predictive condition that increased the risk to develop Alzheimer's disease (AD).
- Depression increases persistence for mild cognitive impairment and is considered as an additional risk factor for conversion to Alzheimer's disease (AD) in Mild cognitive impairment.
- Family physicians are essential to effective dementia care

Recommendations:

1. Family physicians can influence dementia rates by working with patients to manage risk factors.

2. The current evidence is insufficient to assess the benefits versus harms of screening for cognitive impairment in older adults.

3. Family doctors should use brief screening tests when dementia is suspected

4. Screening of depression is an important part in dementia care.

5. Healthy lifestyles can reduce the risk of developing Alzheimer's disease and may be protective.

6. preventing and managing depression reduces the risk of cognitive decline in dementia and delay the conversion to Alzheimer's disease.

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