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Advances in Dementia Research

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Meet the editor

Dr. Ghulam Md. Ashraf is currently working as an associate professor at King Fahd Medical Research Center, King Abdulaziz University, Saudi Arabia. His current research interest covers proteomics, neurobiology, cancer, and nanobiology. He has to his credit 164 publications ranging from peer-reviewed journal articles, books, and book chapters published with scholarly publishers (total citations: 1600, h-index: 20, i10-index: 42). Dr. Ashraf is involved in an editorial capacity in many internationally reputed journals, and has been involved in seven research projects funded by various agencies in Saudi Arabia. He is a member of several renowned professional associations and organizations. Dr. Ashraf received his PhD in Biochemistry from Aligarh Muslim University, India, in 2010.

Contents

Preface

Advances in Dementia Research provides a comprehensive overview of Alzheimer's disease. It has been found that the presence of the components of metabolic syndrome in an earlier life, especially middle age, increases the risk of Alzheimer's disease, although it has recently been suggested that these components may begin the progression to dementia as early as adolescence. This book represents the association between the components of metabolic syndrome and Alzheimer's disease. Vascular dementia is the second most common cause of dementia after Alzheimer's disease. The basic understanding of vascular dementia and its molecular mechanisms is a complex phenomenon. Vascular dementia associated with neurodegeneration and cognitive impairments is caused by multiple complications of the neurovascular system. This book attempts to explore the recent advancements of enzyme targets for the management of vascular dementia. Furthermore, this book highlights the effectiveness of social recreational programs as an example of a recovery intervention for persons with dementia that focuses on reducing the risk of social isolation associated with dementia. Together the insightful research presented in this book provides valuable information for those involved in this area, including neuroscientists, researchers, medical professionals, academicians, and upper-level students, as well as industry professionals.

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Chapter 1

Introductory Chapter: Alzheimer's Disease—The Most Common Cause of Dementia

Md. Sahab Uddin and Ghulam Md. Ashraf

1. Introduction

Alzheimer's disease (AD) is the utmost common form of dementia, a usual term for memory defect and other cognitive impairments that seriously affect daily life [1]. This degenerative disease is accountable for 60–80% of dementia cases. AD is not a typical part of normal aging. The supreme well-known threatening factor is aging, and the mainstreams of people with AD are 65 years and older [2]. In fact, AD is not considered as a disease of adulthood. AD and other types of dementia affect a predictable 1 in 14 persons over the 65 year of age and 1 in every 6 persons over 80 years of age. But, about 1 in every 20 cases of AD affects people with in age ranging 40–65 years, which is called early-onset AD.

AD is a progressive disease that deteriorates over time, and symptoms of dementia steadily exacerbate. In its initial stages, memory defect is mild, but over a number of years in late-stage, AD patients lose the aptitude to convey a message and reply to their surroundings [3]. AD is the sixth foremost cause of death in the USA. Patients with AD may live an average of 8 years after the symptoms are visible to others, but the survival rate is higher; it can range from 4 to 20 years, based on aging and other health situations [4].

AD is still incurable, but current treatment strategies can momentarily reduce the deterioration of the symptoms and progress of the quality of life of the patients. Today, there is a universal effort to find better ways to treat the development and progression of AD. The purpose of this chapter is to give an overview of AD.

2. Alzheimer's and the brain

The brain has billions of nerve cells called neurons attached with each other to construct communication network. There are several groups of nerve performing specific jobs like thinking, learning, remembering, smelling, etc. [5].

To perform their job, like the receiver of supplies, generation of energy, construction of equipment, and disposal of waste, neurons operate like tiny factories. Brain cells also reserve, process information, and connect with other cells. In order to keep all of these running, they require a huge amount of fuel and oxygen as well as coordination.

Efforts of a lot of researchers are going on to untangle the complicated changes of the brain happened in the early stage and advancement of AD (**Figure 1**).

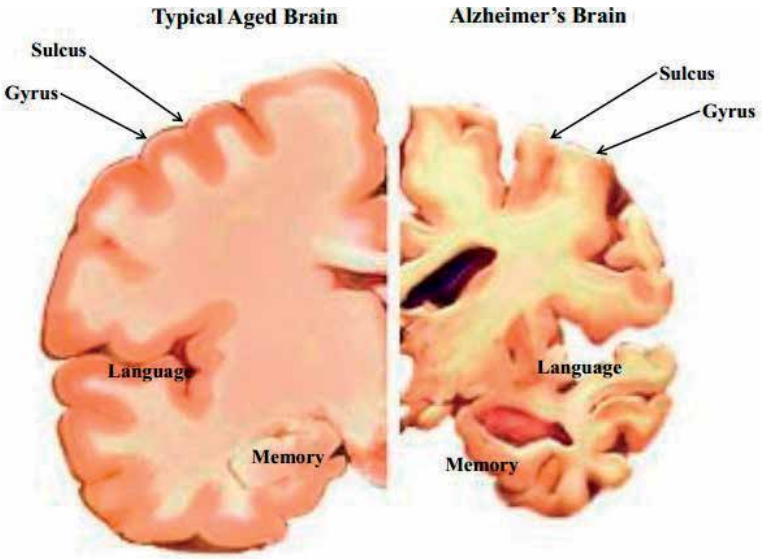

Figure 1.
The normal aged brain and the brain of an Alzheimer's patient.

It seems feasible that brain degradation starts a decade or more before memory deficit and other cognitive dysfunctions actually appear. Throughout the early stage of AD, patients do not display any symptoms; however, cytotoxic turns do appear in the brain. Senile plaques (SPs) and neurofibrillary tangles (NFTs) are formed due to abnormal deposition of proteins that result in discontinued function of neurons, failed internetwork, and ultimately neuronal death [6].

The hippocampus is the part of the brain having the vital role in generating memories and seems to be affected initially, and later, the damage spreads out to all other parts of the brain [7]. As a result, the brain starts to shrink. Moreover, significant widespread damage and shrunk in the brain tissues appear in the final stage of AD.

3. Causes of Alzheimer's disease

The main reason of AD is not completely understood till now. Approximately 70% reason for Alzheimer's is genetic [8, 9]. A number of factors are supposed to raise the risk of developing the condition such as:

- Family history
- Untreated depression
- Lifestyle-related factors linked with cardiovascular events

4. Signs and symptoms of Alzheimer's disease

With age, changes in the brain as well as rest of the body cells are obvious. Most of us in general notice such kind of changes by facing difficulties like losing the capacity of thinking and/or remembering certain things.

Difficulties in remembering newly known things and information are the most usual early feature shown in AD, because in the initial stage of Alzheimer's changes occur in the area of the brain involved in learning [10]. In advance stage of the AD, brain changes cause generation of progressively awful symptoms, including disorientation, behavior, and mood changes; deepening skepticism about events, location, and time; baseless doubts about family, friends, and professional caregivers; serious loss of memory; and difficulties in the everyday jobs like swallowing, speaking, walking, etc. [11].

There are numerous threatening signs and symptoms of AD. Every people may notice one or more of these signs in a diverse degree:

- Memory deficit that interrupts daily life
- Alterations in planning or problem solving ability
- Trouble in doing routine works at home and work
- Misperception about place and time
- Trouble in the visualization and spatial dealings
- Difficulty in speaking or writing
- Forgetting things and reducing the capacity to repeat phases
- Reduction of judgment skill
- Alteration of personality and mood
- Separation from social events or works

5. Pathological Hallmarks of Alzheimer's disease

The SPs consist primarily of amyloid β (Aβ) and neurofibrillary tangles (NFTs), consist of tau proteins are the abnormal structures considered as suspects for the damage of brain cells. Aβ is derived from the amyloid precursor protein (APP), which is cleaved by beta secretase and gamma secretase, and NFTs are the aggregates of hyperphosphorylated tau protein [12].

A lot of people develop plaques and tangles along with age, as shown by autopsy studies. Patients with Alzheimer's have the potential to spread into far more areas by plaques and tangles in a foreseeable pattern [5]. In fact, first, these pathological hallmarks appear in the area of memory before spreading to the other regions.

The impact of plaques and tangles in AD still remains unclear. Most of the researchers believe that they somehow play a complex pathogenic role in AD to block the network of brain cells and interrupts the processes required for cell survivals [13]. The destruction and death of nerve tissues are the causes of failure of the memory, personality changes, and other difficulties to carryout usual activities in everyday life and other symptoms of AD.

6. Alzheimer's and typical age-related changes

In case of most people, the sporadic decrease in memory is measured as a typical part of the aging, which is not a threatening sign of stern mental failure or the onset of dementia (**Table 1**).

Signs of Alzheimer's/dementia	Typical age-related changes
Poor judgment and decision-making	Making a bad decision once in a while
Inability to accomplish a budget	Missing a monthly payment
Losing trail of the date or the season	Forgetting which day it is and remember it later
Trouble having a conversation	Occasionally forgetting which word to use
Misplacing things and being unable to retrace steps to find them	Losing things from time to time

Table 1.
The differences between AD and typical age-related changes [14].

The memory deficits that are usual amid older adults and usually are not reflected as caution signs of dementia is presented below:

- Becoming easily blurred
- Rarely forgetting an appointment
- Entering into a room and forgetting the reason for entrance
- Unable to recover info that are on the tip of the tongue
- Worried to remember just read info or the details of a chat
- Abruptly forgetting where things of common use (such as keys) have been kept
- Fail to recall names of acquaintances or difficulty in one memory with a similar one, such as calling a grandson by his/her son's name

7. Diagnosis of Alzheimer's disease

The person with age group older than 80 years if diagnosed with AD can survive at least 3–4 years, whereas younger peoples can stay alive usually about more than 10 years [15].

Various methodologies and tools are deployed by the physician to identify the actual problem such as the possible AD or probable AD.

To diagnose AD, usually physicians may:

- Ask the patient and the family member or close contacts about the health status, past medical history, capability to perform daily works, and alteration in behavior and personality
- Conduct tests of memory, attention, language, problem-solving, and counting ability
- Conduct other tests like blood and urine tests, to find other likely reasons for the problem
- Perform the scans of the brain like computed tomography, positron emission tomography, magnetic resonance imaging, or other tests to detect the promising causes for symptoms

These tests are effective to identify how the person's memory and other cognitive functions are altering over time. However, AD can be certainly diagnosed only after the death of the patient, by relating the clinical events with the autopsy of the brain.

If a person has memory problems, they must consult a physician related to their problems so as to facilitate the physician to diagnose whether it is AD or any other issues such as Parkinson's disease, stroke, sarcoma, adverse effects of medicines, or a non-Alzheimer's. Few of these diseases are curable and conceivably revocable.

If the disease is diagnosed in its early phase, it may be treatable and very helpful for future plans such as economic and legislative matters, becoming habituated to living measures and developing the buttress networks.

Furthermore, the participation of patients in clinical trials is also one of the advantages of early diagnosis because it makes newer researches and treatments for AD.

8. Treatment of Alzheimer's disease

Due to the complexity of AD, its treatment by only one drug or other medication is not possible. Therefore, the pivotal strategy is to help the patient to maintain intellectual function and behavior as well as mitigate the specific concerns like reduction of memory deficits [7]. Newer therapies are expected to be establish by researchers to target the peculiar genetic, molecular and cellular mechanism which can stop the intrinsic genesis of the disease.

Psychological treatments like cognitive stimulation therapy are also helpful to improve memory, language ability as well as problem resolving talents.

9. Prevention of Alzheimer's disease

The exact reason for the pathogenesis of AD is still anonymous [16]. But researchers put their efforts to minimize hazards or postponement of the onset of dementia, and suggested the following that can reduce the chance of dementia:

- Stopping smoking
- Reducing alcohol consumption habit
- Eating a balanced diet as well as maintaining weight
- Staying physically and mentally fit and active

Not only AD, these events have other health aids, such as reducing the risk of numerous diseases especially cardiovascular disorders and improving the overall health status.

10. Research and progress

Nowadays, studies are focusing to detect the exact etiology of plaques deposition, tangles formation, and associated with other biological landscapes of AD [7]. The development and progress of Aβ and NFTs in the living brain, as well as the change in brain anatomy and activity, can be observed with the help of existing brain scan techniques. With the help of the results obtained by studying the alterations that take place in the brain along with body fluids, researchers evaluate the

initial steps involved in the disease progress prior to the appearances of Alzheimer's symptoms that give information about the root cause of AD as well as also facilitates its diagnosis.

The utmost enigma of AD is why it mostly attacks older is still a great obscure [7]. Research on the typical aging of the brain is making this question transparent. Researchers are learning how age-linked variations in the brain may damage neurons and contribute to AD. The alterations caused due to atrophy (i.e., shrinking) in some area of the brain, infections, release of free radicals as well as the mitochondrial defect (some deformities in the powerhouse of the cell causes unnecessary breakdown of energy molecules and results in the loss of energy). These alterations in old age people enlighten the reason why adults are susceptible to AD.

11. Conclusion

Current studies are working to elucidate copious aspects of AD and dementia. About 90% of what we know about AD has been discovered in the last 20 years. The greatest auspicious progress in AD research is how it affects the brain. There is hope that this superior understanding of the pathogenic mechanism will lead to better treatment strategy with minor adverse/side effects. At present numerous latent approaches are under study worldwide.

Conflict of interest

The authors proclaim that they have no competing interests.

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Chapter 2

Recent Advance of Enzyme Targets for the Management of Vascular Dementia

Arunachalam Muthuraman, Narahari Rishitha and Johurul Islam

Abstract

The basic understanding of vascular dementia (VaD) and their molecular mechanisms are a too complex phenomenon. VaD associated neurodegeneration and cognitive impairment are due to multiple complications of the neurovascular system. The progress of VaD is due to the central and/or peripheral pathophysiological process of the neurovascular system. There are limited nootropic agents are employed for the treatment of VaD. Moreover, the explored nootropic agents act on multiple targets such as receptors, enzymes, ion channel, free radicals, cytokines, chemokines, and apoptotic proteins. However, the enzyme targets, especially acetylcholinesterase inhibitors played a crucial role in the management of cognitive disorders. The pathogenesis of VaD is involved in the vascular complication and neurodegenerative process. Hence, the enzymatic regulation of neurovascular complication is expected to prevent the VaD. The present chapter attempts to explore the recent advancement of enzyme targets for the management of VaD.

Keywords: cognitive dysfunction, enzymes, memory, neurodegeneration, neurovascular complication, vascular dementia

1. Introduction

Vascular dementia (VaD) is one of the leading factors for the changes in quality of life. It is declining the thinking ability [1]. The major etiology in the pathogenesis of VaD is blockage of cerebral blood vessels and/or reduction of regional and global cerebral blood flow [2]. This leads to depriving the brain cells for vital oxygen and energy by rising of free radicals; reduction of endogenous anti-oxidants and their regulatory enzymes [3]. The aging is another factor to develop neurovascular complications [4]. The developing country like India faces the serious complication of vascular dementia. India has more than 75 million populations older (above 60 years) [5]. This age group; dramatically grow 7.5% of the population in every decade [6]. Therefore, demanding care for older people is growing day by day. The certain neurological disorders mainly occur in old age like dementia and Alzheimer's disease (AD); however, the specialized medicines and improvements quality of life remains limited and challengeable [7]. Furthermore, VaD is mainly due to the various changes in vascular compartments in the brain. It is classified as cortical vascular dementia; subcortical ischemic dementia; strategic-infarct dementia;

hypoperfusion dementia; hemorrhagic dementia; and dementias of specific pathology of cerebral artery [8]. The primary hallmark of the VaD is the development of cognitive deficits and impairment of functional abilities. The more specific diagnostic criteria for VaD described by Diagnostic Manual of Mental Disorders, 4th edition (DMS-IV) criteria [9]; and National Institute of Neurological Disorders and Stroke—Association International pour le Recherché at L'Enseignement en Neurosciences (NINDS-AIREN) criteria [10]. The DSM-IV criteria have good sensitivity, but low specificity. Whereas the NINDS-AIREN criteria are the most specific to all available criteria and most commonly used in clinical research [11]. The clinical features of VaD are determined by the size, location, and type of cerebral damage. The classical clinical features of VaD are the abrupt onset of memory, stepwise deterioration of mental function, fluctuating learning course, abnormalities of the motor and sensory response, gait changes and development of urinary incontinence [11].

Currently, the nootropic agents are used to treat the VaD [12]. Thus, the prescription of nootropic agents such as central nervous system (CNS) stimulants (amphetamine, methylphenidate, caffeine and nicotine) [12]; Racetams [positive allosteric modulators of AMPA receptors and cholinergic systems such as piracetam, oxiracetam and aniracetam) [13, 14]; and miscellaneous such as L-theanine, tolcapone, levodopa, atomoxetine, *Panax ginseng*, *Ginkgo biloba*, *Salvia officinalis* [15], omega-3 fatty acids, folate, vitamin B_6, B_{12}, and E [16, 17]; pramipexole, guanfacine clonidine, and fexofenadine are documented to produce the ameliorative effect in neurocognitive disorders like vascular dementia [18, 19]. However, it produces the potential adverse effects and chronic usage it shown less efficacy [20]. Various nootropic agents are acts via multiple cellular targets like receptors, enzymes, ion channel, free radicals, cytokines, chemokines and apoptotic proteins [21]. However, the enzyme targets are shown to produce the better beneficial effects in neurocognitive disorders like acetylcholinesterase inhibitors carbamates (physostigmine, neostigmine, pyridostigmine, ambenonium, demecarium, and rivastigmine) [22, 23]; phenanthrene derivatives (galantamine) [24]; donepezil; tacrine, edrophonium and huperzine A [25]. Therefore, this book chapter is focused to explore the role of enzymes in the pathogenesis of VaD and also discussed the recent advancement of enzymes targets based medicines for the management of VaD disorders.

2. Risk factors of vascular dementia

Globally, the aging peoples are suffering from dementia and AD and increase the burden to maintain the quality of life. The effective medicines for the treatment of VaD are not available and conventional nootropic medicines are relived the VaD symptomatically [26]. The factor medication for the pathogenesis of VaD is reducing the risk of cognitive decline effects. The main modifiable risk factors for VaD are lack of exercise, smoking, hypertension, obesity, diabetes mellitus, and chronic depression. The maintenance of this modifiable risk factors are supporting to prevents the pathogenesis of VaD and enhances the cognitive reserve function & quality of healthy life [27].

3. Characteristic features of VaD

The main characteristic features of VaD is described the problems of reasoning, planning, judgment, memory and thought processes. It occurs by damage central nervous system; and lack of cerebral blood circulation; and depriving of

the brain of vital oxygen and nutrients. Other than hyperglycemia, hypertension, hyper-lipidemia, and smoking; certain diseases also cause VaD like heart disease and stroke [28]. In the acute stage, confusion, trouble in attention; reduction of thinking ability; analyzing the ability of situation; deciding ability; restlessness; agitation; abnormal gait posture; frequent urination and/or inability to control the passing of urine; depression; and apathy. This characteristic feature of VaD develops the gradual manner like AD. The two main characteristic features are important for the pathogenesis of neurovascular disorders like VaD; one is arterial infarction (stroke) associated blocking of cerebral artery [28]. Some strokes are not producing noticeable symptoms of VaD. Whereas, it enhances the risk of VaD; and it is called multi-infarct dementia. Another feature of VaD is the chronic narrowness of cerebral blood vessels. It occurs by long-term damage of brain blood vessels by aging, high blood pressure, abnormal cholesterol deposition in the cerebral blood vessels, diabetes and brain hemorrhage [29]. These features are changes the wear and tear principles of cerebral blood vessels leads to cause the VaD.

4. Enzymes as a target for VaD

Various enzymes are identified in the regulation of neurovascular peptide action and it can prevent the cognitive disorders. Mainly drug target is focused on the receptors; ion channels; and nuclear proteins. There are limited drugs are explored in the enzymes based drug therapy for the neurovascular disorders [30]. Enzyme targeted medicines effectively prevent the various disorders such as inflammation (cyclooxygenase inhibitor); peptic ulcer (proton pump inhibitor); heart failure (sodium-potassium ATPase inhibitor); hypertension (angiotensin-converting enzyme inhibitor); depression (monoamino oxidase inhibitor); including memory disorder (acetylcholinesterase inhibitor). This chapter will open the "Pandora's box" for the newer drug discovery for the treatment of VaD via enzyme inhibitors and modulators.

4.1 Acetylcholinesterase

Acetylcholinesterase (AChE; EC 3.1.1.7) also called as acetyl hydrolase. It belongs to carboxyl esterase family of enzymes. It predominantly acts on multiple organ systems including central as well as the peripheral nervous system [31]. The primary action of AChE is a breakdown of the acetylcholine to choline esters. In addition, it acts as neurotransmitters and alters the neuromuscular junctions and synaptic junctions. In addition, the central cholinergic system is plays a key role in the neuromodulatory action; vasomotor control; cerebral circulation of blood; and cognitive function. The basal prosencephalon and routes of their projections are the main areas for the cognitive function [32]. The vascular lesion of this area alters the cholinergic neuronal pathways via acetylcholinesterase and cholinergic neurotransmitter action. The denervation of this cholinergic neuron plays a role in the development of cholinergic hypofunction and vascular dysfunction. Which leads to enhance the VaD associated cognitive dysfunction [32]. The administration of cholinesterase inhibitors like donepezil, galantamine and rivastigmine are symptomatically relieved the symptoms of VaD in human [33]. Similarly, all three agents are shown beneficial effects in mild to the moderate condition of Alzheimer disease (AD) type of VaD. Even though, FDA has not approved the cholinesterase inhibitors for the treatment of advanced stages of the AD; due to lack of efficacy and tolerability. Hence, some of the research reports suggest that cholinesterase inhibitors might

be useful for the other types of dementia like vascular dementia and dementia with Lewy bodies.

4.2 Amyloid-β-peptide alcohol dehydrogenase

ABAD (EC: 1.1.1.178) enzymes also belong from oxidoreductase enzyme. This alcohol dehydrogenase is activated by amyloid-β peptide and it affects cellular functions. The extracellular amyloid-β peptide is interacting with cell surface receptors and its trigger the intracellular signaling cascades. In addition, the amyloid-β peptide is interacting with specialized mitochondrial enzyme i.e., amyloid-β peptide-binding alcohol dehydrogenase (ABAD) [34]. The binding properties of the amyloid-β peptide to ABAD have altered the metabolic properties of the neuronal cell, and promotes mitochondrial free radicals synthesis via modulating the electron transport chain [35]. The activation of ABAD is required dinucleotide cofactor i.e., nicotinamide adenine dinucleotide (NADH). The overactivation of ABAD enhance the amyloid-β rich environment leads to accelerates the cell stress leads to raising the levels of 4-hydroxynonenal-lysine; malondialdehyde-lysine; and induction of DNA fragmentation of the neurovascular system. In addition, ABAD induces the utilization of ketone bodies by neurovascular cells by promoting the conversion of acetyl-CoA to tricarboxylic acid cycle. This reaction also enhances the nutritional and/or metabolic stress [36]. The ABAD mutated (upregulated) transgenic mice are shown the amyloid-β peptide-rich environment leads to accelerates the spatial learning and memory impairment via cellular oxidative stress [37]. Hence the Aβ and their target enzymes ABAD are contributed in the pathogenesis of neurovascular disorders including VaD. Therefore, the authors review the evidence that the prevention of Aβ binding to ABAD is a drug target for the treatment of AD. Therefore, the ABAD can be considered as a newer target for the attenuation of VaD.

4.3 Angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE; EC: 3.4.17.23) is one of the families of hydrolase enzyme. ACE is a major component for the renin-angiotensin system (RAS). It plays a key role in the pathogenesis of blood pressure. ACE converts the angiotensin I (AT-I) to angiotensin II (AT-II). AT-II peptide is a potent endogenous vasoconstrictor. In addition, AT-II peptide and their receptor also play a various pathophysiological action on the central nervous system [38]. The brain-derived ACE has a role in the alteration of cerebral hemodynamics and execution of cognitive functions. Further, some literature revealed that anti-hypertensive medicines such as ACE inhibitors are shown the improvement of cognitive function via reduction of neurovascular damage. The inhibitor of centrally acting ACE enzymes like captopril, fosinopril, lisinopril, prinivil, perindopril, ramipril, and trandolapril is slow down the cognitive deterioration in human [39].

Furthermore, ACE interferes with bradykinin pathway in lung system and epithelial cells of the renal tissue. Currently, ACE is identified for the progress of neurodegenerative process via alteration of amyloid-β peptide metabolic and catabolic events. The treatment of ACE inhibitors is documented to produce the neuroprotection and prevention of neurodegenerative process [40]. The administration of central acting ACE inhibitor i.e., captopril and perindopril are produced the ameliorative effect in late-onset AD type of VaD. Moreover, another ACE inhibitors i.e., enalapril and ramipril are also controlled the dementia-related cognitive dysfunction [41]. Therefore, the ACE enzymes are playing a key target for the discovery of newer ACE inhibitors for VaD treatment.

4.4 Endothelin-converting enzyme

Endothelin-converting enzyme (ECE) belongs from hydrolase family of enzyme and it is encoded by the ECE gene in human. The function of ECE is involved in the proteolysis process of endothelin peptides. There are three biologically active ECE are identified i.e., ECE-1; ECE-2; and ECE-3. The ECE-1 are catalyzed the biologically active endothelin-1 (ET_1); endothelin-2 (ET_1); and endothelin-3 (ET_1) peptides. The ECE-1 is primarily originated from endothelial cells; whereas, ECE-2 is originated from neuronal cells. Both ECEs have induced the ET-1 peptide production and cleavage the amyloid-β peptides [42]. The treatment of amyloid-β_{40} and amyloid-β_{42} peptides enhances the ECE-2 gene expression and release of ET-1 in neurovascular tissue. In addition, the endogenous superoxide dismutase prevents the amyloid-β_{40} induced release of ET-1. In AD patients, ECE_1 induces the production of endothelin-1; and free radical is enhancing the cerebral vasoconstriction and reduction of cerebral blood flow. The chronic reduction of cerebral blood flow is one of the hallmarks in the pathogenesis of VaD [43]. The ECE hydrolyzes the bioactive peptides like bradykinin, neurotensin, substance P and insulin B chain. In addition, the over-activation of ECEs are involved in the alteration of amyloid-β degradation. The ECE are altered the neurovascular function of various brain areas such as cerebral cortex, hippocampus, amygdala, basal forebrain nuclei, diencephalon, brain stem, cerebellar hemisphere including hippocampus neurons. The clearance of amyloid β (Aβ) occurs by three major vasopeptidases i.e., neprilysin; ECE-1 and ECE-2. This clearance of amyloid β reactions occur by time; concentration and cellular environment dependent manner. And it accelerates the cellular metalloproteases enzymes leads to alter the vascular function and enhances the pathogenesis of VaD [44].

In addition, the non-selective dual endothelin-A (ET-A) and ET-B receptor antagonist i.e., bosentan ameliorates diabetes induced vascular endothelial dysfunction and vascular dementia in rats [45]. Similarly, it also attenuates the hyperhomocysteinemia, β-amyloid and renovascular hypertension-induced vascular dementia in rats. Further, the administration of selective endothelin ET-A receptor antagonist i.e., ambrisentan attenuates the L-methionine-induced vascular dementia in rats [46]. ECEs inhibitors can control the accumulation of ET-1 peptide and activation of ET receptors. Therefore, ECE regulators, especially ECE-1 can be a key target for the management of VaD.

4.5 Histone deacetylase

Histone deacetylase (HDAC; EC: 3.5.1.98) is belonging from the hydrolases type of enzymes. HDAC removes the acetyl groups ($O=C-CH_3$) from ε-N-acetyl lysine amino acid of the histone proteins. And, it makes the tight wrapping of DNA to histone proteins [47]. This process supports the regulation of DNA expression via the cyclic action of acetylation and de-acetylation events. Histone acetyltransferase is opposite the histone deacetylase action. In addition, lysine deacetylases (KDAC) enzymes are similar to that of HDAC action; but it also produces the non-histone protein-mediated DNA expression actions. The primary action of HDAC action is a modification of histone tails via modification of lysine and arginine amino acids. These changes make the positive charges environment on histone tails and interact negatively charged phosphate groups of DNA backbone [48]. Acetylation process is neutralizing the positive charges of the histone tail leads to decreases the DNA interactions. In this case, histone proteins allow the chromatin expansion; permits the gene transcription. In a paradox, HDAC opposite this all reaction sequences. In a

normal cell, HDAC is regulated the cellular processes via cell growth; cellular apoptosis; and cell cycle events. In pathological conditions, it stimulates the cancer cell growth; and actives the chronic myeloid leukemia progress. The hyperacetylation of chromatin is causing the abnormal transcription process [49].

There are 18 numbers of HDACs are identified in human i.e., $HDAC_1$ to $HDAC_{18.}$ It is further divided into four classes i.e., class I: Rpd3-like proteins ($HDAC_{1–3}$; and $HDAC_8$); class II: Hda1-like proteins ($HDAC_{4–7}$; $HDAC_9$; and $HDAC_{10}$); class III: Sir2-like proteins ($SIRT_{1–7}$); and class IV protein ($HDAC_{11}$) [50]. HDAC inhibitor-like valproic acid is used for psychiatric disorders including epileptic disorders. Another, HDAC inhibitors *i.e.,* vorinostat and romidepsin are approved for the treatment of cutaneous T cell lymphoma [51]. Trichostatin A (potent HDAC inhibitors) are used for neurovascular disorders like stroke; AD; and VaD. The non-selective inhibitor of HDACs i.e., sodium butyrate attenuates the heavy metal i.e., arsenic metal; and streptozotocin-induced endothelial dysfunction and VaD in rats [52]. Currently, the administration of sodium butyrate also ameliorates the ischemia-induced vascular dysfunction in aged female rats [53]. Various HDAC inhibitors are documented to produce the neuroprotection against multiple and variable type of brain injury such agents are suberoylanilide hydroxamic acid (SAHA); hydroxamic acid derivatives (ITF2357); valproic acid (VPA); trichostatin A (TSA); sodium 4-phenylbutyrate (4-PBA); 4-dimethylamino-N-[5-(2-mercaptoacetylamino)pentyl]benzamide (DMA) [54]. However, the effect of these agents in the management

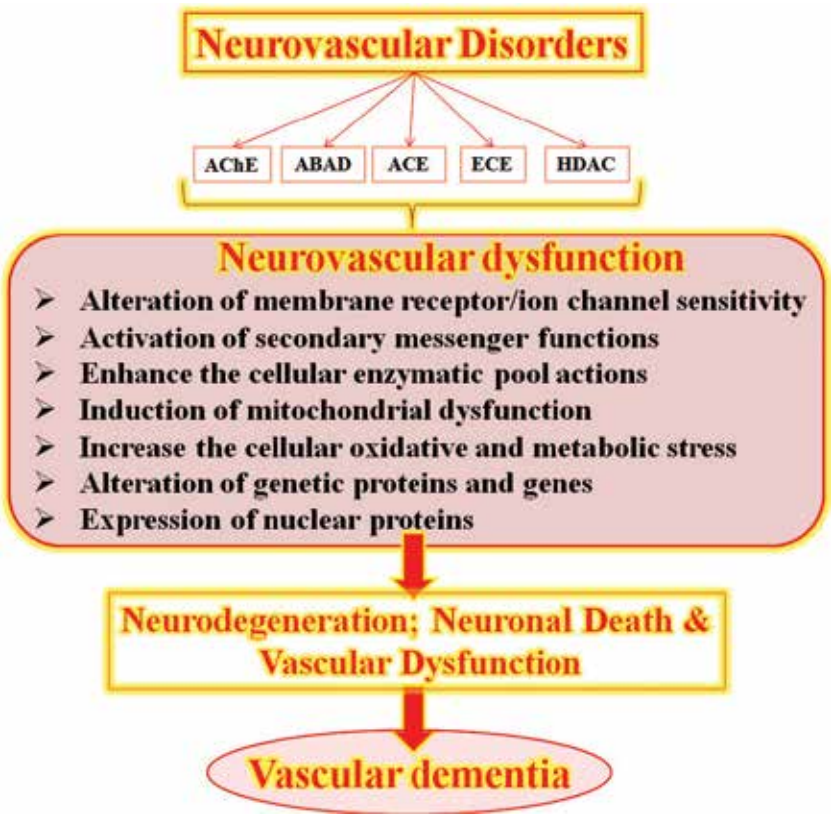

Figure 1.
This illustration revealed that, the role of neurovascular enzyme alteration for the alteration neurovascular dysfunction; neurodegeneration; neuronal death; and vascular dysfunction associated with vascular dementia. Abbreviations: AChE, acetylcholinesterase; ABAD, amyloid-β-peptide alcohol dehydrogenase; ACE, angiotensin converting-enzyme; CART, carnitine acetyltransferase; ECE, endothelin-converting enzyme-1; NOX, nicotinamide adenine dinucleotide phosphate oxidase; and HDAC, histone deacetylases.

of VaD and endothelial dysfunction is not explored yet. HDAC inhibitors are identified as neurovascular protective agents and prevention of VaD. Hence, HDAC inhibitors need to explore in the management of VaD disorders. The role of neurovascular enzyme targets and their mechanism for the alteration neurovascular dysfunction; neurodegeneration; neuronal death; and vascular dysfunction associated vascular dementia is illustrated in **Figure 1**.

5. Future perspectives

Based on the available literature, it concluded that enzymes targets can treat the neurovascular disorders via prevention of endothelial dysfunction; neuroprotection; enhancement of neuronal plasticity; and anti-apoptotic action. In addition, these enzymes targets are also regulated the neuronal as well as vascular growth factor via epigenetic modification and controlling of pre and post-translational protein modifications. Functionally, these enzymes modulators are improved the neurocognitive functions in AD, PD, stroke conditions including VaD in animals as well as in patients. Currently, the various enzymes are identified their roles; physiological & pathological functions; involvements in the neurovascular system; identification of endogenous and exogenous substrates; and their modulators. However, the limited enzyme modulators only tested in animals. Still need more discoveries to develop the enzymes modulators for the above enzymes targets with their specificity, potency and enhanced functionality. Thus, this book chapter will help to the audience to open the "Pandora's box" for the discovery of novel enzyme targets and modulators for the treatment of neurovascular disorders.

6. Conclusion

Based on this review of the literature, it is concluded that the pathogenesis of VaD is occurred by multiple pathophysiological events. However, literature shown that enzymes targets are contributed the development of neurovascular disorders such as VaD. The chronic progress of vascular dysfunction makes the neuronal death; neurodegeneration and cognitive impairment. This book chapter section also showed the evidence of enzymes modulators for the treatment of VaD. However, the specific modulator of this enzymes targeted action is needed to investigate in different pathophysiological conditions of VaD. Further, it also needs to study in clinically relevant animal models and in human subjects.

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Chapter 3

Metabolic Syndrome and Its Biomarkers in the Development and Progression of Alzheimer's Disease and Other Dementias

Teresa Juárez-Cedillo and Susan Drier-Jonas

Abstract

Metabolic syndrome is a condition that includes several components which, individually and together, are steadily increasing in prevalence worldwide. These include obesity, dyslipidemia, hyperglycemia, and hypertension. On the other hand, Alzheimer's disease, one of the family of dementias, is considered a disease of the elderly, whose numbers are also increasing. However, it has been found that the presence of the components of metabolic syndrome in earlier life, especially middle age, increases the risk of Alzheimer's disease, although it has recently been suggested that these components may begin the progression to dementia as early as adolescence. The full pathophysiology of Alzheimer's and the mechanisms by which metabolic syndrome affects it are not fully understood to date. The present chapter examines the association between metabolic syndrome and Alzheimer's disease and the association between the components of metabolic syndrome and Alzheimer's. The authors also represent the genetic involvement in this association, since various genes have been found to be common to both disorders.

Keywords: metabolic syndrome, Alzheimer's disease, biomarkers

1. Introduction

Metabolic syndrome is a medical condition that includes obesity, dyslipidemia, hyperglycemia, and hypertension. It and its components have been recognized as an important risk factor for cardiovascular disease, both macrovascular and microvascular. Given the worldwide epidemic in obesity and diabetes, this syndrome has received serious attention in recent years, although the condition has been studied since it was first described by G. Reaven in 1988 [1]. Metabolic syndrome has been linked to the risk of cardiovascular disease (CVD) and, more recently, to neurodegenerative diseases, including cognitive decline and dementia, which include Alzheimer's disease (AD) [2–4]. The complex relation between metabolic syndrome and dementia is not well understood and remains elusive and controversial. Differences in age, definitions, and sample size have further obscured the truth.

Just what is Alzheimer's disease? Alzheimer's disease is considered a chronic neurodegenerative illness affecting the cerebral cortex and hippocampus that lasts 8–10 years but which has a preclinical period of 20–30 years. AD is a growing health

concern, given the increase in elderly worldwide. Surprisingly, this disease can recede in individuals over 98 years of age [5]. Currently, it is estimated that 1 in 9 adults in US suffers from this disease, and that number is expected to grow by 40% by 2025 [6, 7]. AD is characterized by two factors: neuron plaques made up of amyloid beta (Aβ) protein and phosphorylated tau protein, which forms altered structures and leads to intercellular neurofibrillary tangles. Amyloid-β oligomers have been shown to cause tau phosphorylation in vitro, which would lead to neurodegeneration. In addition, it has been suggested that amyloid-β also induces tau pathology in vivo [8]. This infers that the amyloid-β lesions precede the tau phosphorylation. Amyloid-β is found in the mitochondrial membrane. Abnormalities in amyloid-β cause an increase in the production of reactive oxygen species (ROS), leading to oxidative stress and lipid peroxidation in the neurons. This oxidative stress reduces levels of superoxide dismutase in the mitochondria. This alteration, in turn, leads to an increase in hyperphosphorylation of tau. RCAN1 is a protein produced in response to oxidative stress. If RCAN1 is chronically stimulated, may promote neurodegeneration [9].

The pathology of Alzheimer's disease, and various other dementias, includes loss of neuronal connections in the hippocampus and temporal lobes, neurofibrillary tangles (NFTs), amyloid-β (Aβ), and amyloidopathy of the cerebrovasculature [10].

While the exact mechanisms are still not entirely clear, it has been noted that other conditions usually accompany AD, such as cardiovascular disease and metabolic syndrome. In addition, Alzheimer's usually includes various important comorbidities, including white matter lesions; brain hypoperfusion, usually undetected microinfarcts; and cardiovascular dysfunction. Other comorbidities include obesity, diabetes, and hypertension, collectively known as metabolic syndrome [11, 12].

However, the definitions of Alzheimer's disease and other forms of dementia are slowly becoming blurred, which may suggest that dementia, and Alzheimer's disease in particular, is the result of a series of various pathologies which all converge [13]. Results from the Nun Study and Honolulu-Asia Aging Study indicate that a complex set of cerebral alterations determines the progression of clinically diagnosed AD [14]. The complete mechanisms for the progression of dementia are not yet known. Neither is how the components of metabolic syndrome individually and collectively trigger cognitive decline. However, research is currently focusing on various aspects of this association, in order to design better strategies to combat both conditions.

In addition, various genetic factors have been uncovered which are common to both diseases, suggesting an association [15].

The present chapter will look at the effect of the metabolic syndrome, and each of its components, on the presence and progression of Alzheimer's disease and other related dementias. It will also look at the genetic factors which have been suggested as being associated, as they are common to both conditions. The authors will briefly review the association of age to the progression to Alzheimer's disease.

2. Metabolic syndrome and Alzheimer's disease

The twenty-first century has seen a surge of interest in the association between metabolic syndrome and dementia, specifically, Alzheimer's disease. Given the epidemic of metabolic syndrome and its components (obesity, diabetes, hypertension) worldwide, and the fact that populations are living longer and therefore more prone to age-related diseases, this is not surprising. There is mounting evidence that the presence of metabolic syndrome, or of its components, increases the risk of AD. Although the exact physiopathology of AD is not completely understood, various studies have discovered links between these two conditions.

In the North Manhattan study, each of the components of metabolic syndrome was measured for the risk of dementia. Elevated levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF) was associated with the risk of dementia, as were HDL-cholesterol and the presence of diabetes, although in univariate analysis high blood pressure also associated. This study suggested that metabolic syndrome be considered as a risk factor as a whole, even when the individual components did not significantly increase the risk [16]. Various studies have stated that the greater the number of components of metabolic syndrome present, the greater the risk of dementia [16, 17].

Some studies have found that metabolic syndrome is a risk factor for dementia up to a certain age (reports vary from 65 to 80 years as the cutoff point), and then it becomes a protector. However, Fan et al. found that the onset of metabolic syndrome increased the risk of dementia irregardless of the age at onset, meaning that the onset of metabolic syndrome even beyond these cutoff points poses a risk of Alzheimer's disease [18].

Another possible explanation for this enigma was presented by Watts et al., who believe that the relationship between metabolic syndrome and dementia is not linear. They believe that while the metabolic biomarkers at midlife signal the onset of Alzheimer's disease, in the elderly, they are signs and symptoms rather than causes. However, they point out that by then the prolonged effects of metabolic syndrome have already progressed over decades and the systems involved in cognitive function have been altered [19]. Bowler et al. note that, in addition, the elderly are frequently in poor health, including malnutrition, which may mask or overpower the effect of metabolic syndrome [20].

At the same time, a study among Chinese population with mild cognitive impairment found that the presence of three or more components of metabolic syndrome increased the risk of Alzheimer's disease four times and twice as great just with the presence of diabetes [21]. Likewise, a study with Italian population found that the presence of metabolic syndrome in patients with mild cognitive impairment was a predictor of Alzheimer's disease over the 3.5 years of follow-up in their study. They also noted that among the components of metabolic syndrome, hypertriglyceridemia, abdominal obesity, and hypertension were the most predictive of progression to AD [22].

2.1 Obesity and dementia

Obesity has become a worldwide epidemic in recent years. Hand in hand with this growth, attention has turned to the relation between obesity, as measured by body mass index (BMI), and dementia, specifically Alzheimer's disease. Since this is one of the factors of AD that can be controlled, it is important to consider in the timely prevention of progression to dementia.

Obesity impacts dementia not only by limiting blood supply to the brain but also by increasing the number of fat cells, which restricts the white matter of the brain and causes cognitive decline. To put this in perspective, the average human has a total of 5 l of blood. More fat translates into less blood supply for the brain, causing ischemia [23]. In addition, obesity entails a higher concentration of adipokines (fat cells from cytokines). These decrease the brain's white matter, resulting in decreased neuronal connections and brain atrophy. Therefore, obesity as early as adolescence has vascular repercussions later in life, mostly due to the continued inflammation and adipose-related hormone levels [23]. In fact, the presence of obesity in middle age increases the risk for AD in later years twofold, more than hypertension or high cholesterol [24].

Finally, the underlying causes of obesity, such as a diet high in fats and sugars, influence gut microbiota and disrupt the so-called gut-brain axis, resulting in inflammation that ends in neurodegeneration and, again, brain atrophy [23].

Fibroblast growth factor 21 (FGF21) is a hormone that plays an important role in metabolic regulation and has a positive correlation with BMI and obesity. However, in the presence of neuronal dysfunction, FGF21 is released, reducing the damage caused by the neuronal activity. This mechanism is complicated by obesity, which effectively blocks the FGF21 activity, permitting cognitive decline [25].

At a more direct level, obesity causes cerebral hypoperfusion, which increases β-amyloid production which, in turn, causes endothelial dysfunction, terminating in a dangerous cycle that results in the pathogenic changes found in dementia. This occurs due to a rise in levels of asymmetric dimethylarginine, which decreases nitrous oxide, causing oxidative stress. Various studies have shown that dysfunction of the brain mitochondria increases pro-apoptotic proteins (bax and bad) and decreases anti-apoptotic protein (Bcl-2), resulting in brain apoptosis [26].

Increased fat mass and obesity-associated protein (FTO) are responsible for the prefrontal cortex's processing of food stimuli (sight, smell, taste). If FTO is overexpressed, it leads to an increase in food consumption, resulting in obesity. FTO has also been shown to trigger the phosphorylation of tau in the neurons [27].

Given the fact that obesity is a controllable condition, this should be a focus in the prevention of AD and dementia. It should also be remembered that weight loss programs also reduce other risk factors for AD involved in metabolic syndrome, such as dyslipidemia and hypertension. **Figure 1** shows the possible link between obesity and dementia.

2.2 Dyslipidemia and dementia

It has been suggested that high low-density cholesterol (LDL-c) and low high-density cholesterol (HDL-c) as early as midlife contribute to the development of AD later in life. One study found that high total cholesterol (>240 mg/dL) as early

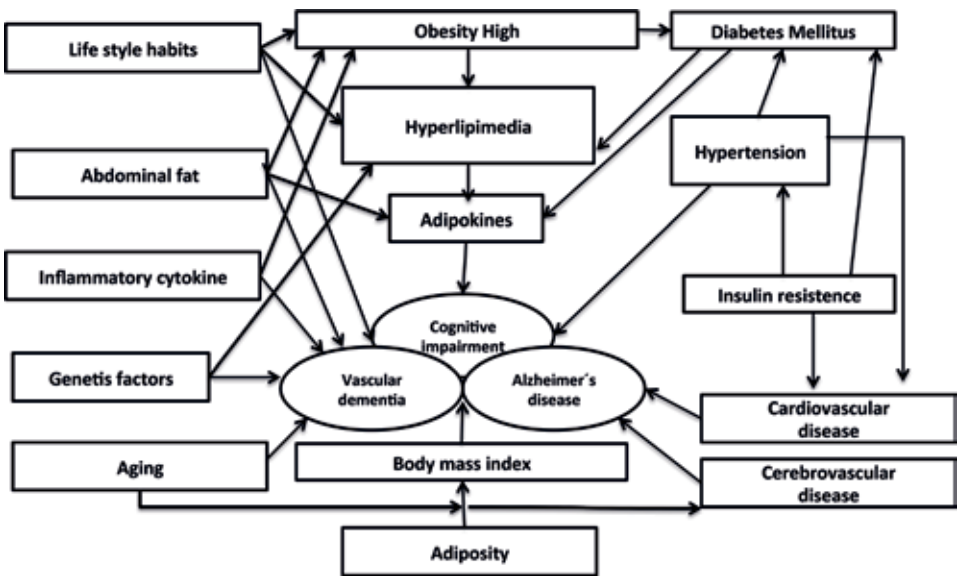

Figure 1.
Possible link between obesity and dementia. Some studies suggest that several factors associated with obesity are also associated with the development of Alzheimer's disease.

as in one's 30s carries a 57% higher risk of developing AD 30 years later [28]. Low LDL-c early in life associates with Aβ plaques later on, a biomarker of AD [29]. This has been proven to be true even in individuals as young as 40 years old [30].

Excess lipids can trigger an increased production of Aβ, leading to the development of plaques. These lipids may also lead to insulin resistance, which will be discussed later on. In addition to the cholesterol, serum triglycerides are a vital factor in this process. Hypertriglyceridemia has been shown to affect brain processes, by altering the peptides crossing the blood-brain barrier, such as decreasing leptin bioavailability. Other affected peptides include galanin (GAL), the opioid peptides enkephalin (ENK) and dynorphin (DYN), and the orexins (ORX) [31]. One study in mice found that by lowering triglycerides, especially triolein, cognitive damage could actually be reversed [32]. The metabolism of cholesterol and lipid proteins in the central nervous system occurs independently from the peripheral nervous system. Processed cholesterol can cross the blood-brain barrier and bind to either LDL-c or HDL-c. These lipids, especially cholesterol, have a key function in the physiopathology of AD. We have seen, and will discuss further, that high cholesterol in middle age increases the risk of AD in later life. However, high levels of cholesterol later in life actually reduces the risk of AD [33].

While exact mechanisms remain elusive, it is very possible that the inflammation that accompanies dyslipidemia is at the root of this association and holds a key role in the pathogenesis of dementia. It should be noted that there are genetic implications, which will be discussed later on. It has been found that mononuclear cells of elderly AD patients have high levels of inflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-16, and IL-18 and tissue growth factor (TGF)-β1. It has been found that these inflammation cytokines, as well as anti-inflammatory IL-10 and IL-13, are found in increased concentrations in the brains of AD patients [34].

In AD, Aβ reaction with microglial receptors can lead to a highly inflamed state [35]. It appears that the activation of the microglial cells unleashes the pro-inflammatory cytokines, leading to increased Aβ and tau hyperphosphorylation. In addition, IL-1β can cause the production of inflammatory factors and has shown to play a variety of roles in neuron damage.

It is widely accepted that obesity incurs systemic inflammation. Hypercholesterolemia is known to increase the levels of inflammatory cytokines. Neuroinflammation and neurodegeneration increase microglial activation. This leads to a further inflamed state, resulting in a vicious cycle. However, lifestyle changes that lower LDL-c and triglycerides and raise HDL-c can help prevent or possibly reverse the cognitive damage.

2.3 Diabetes and dementia

One of the most widespread outcomes of metabolic syndrome is diabetes mellitus. Both type 2 diabetes mellitus (T2DM) and dementia are considered age-related diseases, although, as we will see later on, this assumption may need to be changed. While the full impact of diabetes on cognitive decline and dementia is still not completely known, alterations in cognition begin as early as pre-diabetes [36]. Various domains of the brain have been shown to be affected by T2DM, suggesting that the diabetes negatively impacts the processing networks [37]. However, diabetes has not been directly linked to the neuropathology of dementia. Nevertheless, there are other means by which diabetes may be closely linked to dementia, especially Alzheimer's disease. One of these links may lie in the fact that T2DM usually leads to atherosclerosis, which mediates cognitive decline. Another may lie in the alterations to cerebral glucose metabolism, as suggested by Chornenkyy et al.

[38]. Evidence from studies such as the Baltimore Longitudinal Study of Aging have shown, through autopsy, that glucose metabolism is altered in the orbital and prefrontal cortex, temporal cortex (middle gyrus, parahippocampal gyrus, and uncus), and cerebellar regions in cases of Alzheimer's disease [39, 40]. It is possible that there is an upstream effect and that these alterations in glucose metabolism impact the β-amyloid deposition, a characteristic of AD. In addition, these alterations in glucose metabolism would affect the mitochondria, causing them to release reactive oxygen species (ROS) and triggering apoptosis. The increased ROS, in turn, accelerates the metabolic syndrome while at the same time impacting β-amyloid processing.

Another means by which T2DM may affect AD lies in lipid metabolism. Cholesterol affects the peptide levels in β-amyloids. Increases in cholesterol cause increases in the levels of cholesteryl esters, which in turn increase β-amyloid concentrations [41].

Insulin resistance (IR) is one of the main characteristics of T2DM. Research has increasingly found that IR is a factor in dementia. Much attention is being paid to the inflammatory markers associated with IR, such as interleukin-6 (IL-6) and C-reactive protein (CRP). In fact, Singh-Manoux et al. found that increased IL-6 as early as middle age is a predictor of dementia later in life [42]. It has been suggested that these inflammatory cytokines cause thrombotic vascular events, which then lead to cerebral infarction. Another way in which IR may affect dementia is related to the higher cortisol levels found in T2DM, which have long been linked to cognitive decline and dementia.

Finally, one of the common complications of T2DM is diabetic autonomic neuropathy (DAN). It has been suggested that the presence of DAN signals alterations in the hypothalamus, midbrain, brainstem and cortex. One study found that treatment with plasmapheresis improved performance on cognitive tests, indicating improvement in autonomic nephropathy [43].

2.4 Hypertension and dementia

Hypertension has been identified as a risk factor for cognitive decline. In fact, various studies have associated midlife hypertension with dementia later in life [44, 45].

Left ventricular hypertrophy (LVH) is usually an end result of hypertension. A very recent study has associated the presence of LVH in midlife with the incidence of dementia [46].

It is known that unchecked hypertension leads to microinfarcts and microhemorrhages, which in turn inhibit cognitive function. Hypertension also induces an increase in Aβ peptides in the brain while inhibiting vascular clearance of amyloids [47]. The ensuing accumulation results in amyloid angiopathy, a classic indicator of AD. In addition, these microinfarcts and microhemorrhages cause white matter lesions. A study in 2004 found that patients with hypertension and the resulting white matter lesions did significantly poorer on neurological tests [48]. Unfortunately, this study did not include adequate follow-up to track progression to dementia and Alzheimer's disease.

One important recent study concentrated not on amyloid activity but rather on tau phosphorylation. Raz et al. [49] found that the vascular alterations caused by hypertension promoted tau phosphorylation, leading to cell death and brain atrophy. They explain that chronic hypertension alters the arterial endothelial cell lining, causing hypoxia and changing oxidative metabolism. This in turn triggers an inflammatory cascade that ends in neuronal cell death. The hypoxic hypoperfusion also triggers a neuropathological cycle, which involves the production of free

radicals, activation of microglias, alteration of the blood-brain barrier, and tau hyperphosphorylation.

Several studies have found that the use of antihypertensive drugs, especially diuretics, can reduce the risk of Alzheimer's disease. These studies include the Ginkgo Evaluation of Memory study (GEM) [50] and the Cache County study, a hallmark of study in this area [51, 52]. More research is needed to see if the use of antihypertensive medication and/or diuretics is a therapeutic option for those with a high risk of Alzheimer's.

3. Genetics, metabolic syndrome, and dementia

With the development of genome-wide association studies (GWAS), more information about the association between metabolic syndrome and dementia has become available. By comparing the phenotypes associated with cardiovascular disease and metabolic syndrome with those most common to Alzheimer's disease, researchers have been able to establish common links, and with that information establish the genetic risk factors for metabolic syndrome that also confer risk of Alzheimer's disease [53].

Apolipoprotein E (ApoE) is the major cholesterol transporter in the brain. With the discovery of the ApoE4 allele, a key to the pathogenesis of AD was uncovered. It was found that the presence of this allele associates with the risk of developing AD at a younger age, especially in the presence of ApoE4/E4 homozygotes [54].

However, ApoE2/E3 has a protector effect. In addition, some ApoE4- haplotypes enable the protector effect of lipids on neural membranes, while ApoE4+ impairs this effect [55]. This may help at least to partially explain the difficulty in assigning the role of lipids in AD. Nevertheless, single nucleotide polymorphisms (SNPs) of ApoE have been identified as being related with lipid metabolism (CLU and ABCA7) and with inflammation (CR1 and HLADRB5) [56, 57]. Nevertheless, this situation may not be a permanent one. A case study published by Brown et al. intervened in the case of a 38-year-old man with metabolic syndrome and mild cognitive decline, who came from a family with a background of Alzheimer's disease. He was put on a ketogenic diet and given a program of high-intensity exercise. After 10 weeks, the biomarkers of the metabolic syndrome improved, as did his memory function. Insulin signaling approached normal, indicating that the ApoE4 gene had been effectively silenced [58].

These are not the only genetic markers. A rare variant in TREM-2 shares in the risk of AD [59, 60]. Reduce of the biomarkers of metabolic syndrome showed marked improvement, and his memory improved; expression of SORL1 also leads to Aβ accumulation. In addition, the interaction between SORL1 and ApoE closely associates with an increased risk of AD [61]. Another candidate is sirtuin 1 (SIRT1). It has been suggested that the protein of this gene, together with PGC1α, may help maintain brain function by participating in the regulation of mitochondrial function. This, in turn, activates the endothelial growth factor (VEGF) and conserves the integrity of the blood-brain barrier. At the same time, the aging process in itself promotes reactive oxygen species (ROS), which accumulated and caused mitochondrial dysfunction, lowering VEGF and leading to Aβ deposits, which form plaques and cause Alzheimer's disease [62].

In addition, Zhang et al. recently compared the genetic markers of metabolic syndrome, dementia, and diabetes and found 86 genes common to all 3 diseases, which if combined comprised 43% of the genes known to be associated with dementia, including APOE, APP, PARK2, CEPBP, PARP1, MT-CO2, CXCR4, IGFIR, CCR5, and PIK3CD [63].

Other, less frequent genetic risk factors include phosphatidylinositolbinding clathrin assembly protein (PICALM), CD33, triggering receptor expressed on myeloid cells 2 (TREM2), the ATPbinding cassette transporter ABCA7, clusterin (CLU) and complement receptor type 1 (CR1), all of which are suspected as being involved in the clearance pathways of Aβ [5].

Another important link between metabolic syndromes may lie in microRNA. These tiny RNAs have been accepted as being involved in metabolic syndrome but have also recently been found consistently in Alzheimer's patients. These include hsa-mir-21 (obesity, hypertension, and T2DM), hsa-mir-103^{a} (hypertension and diabetes), hsa-mir-17 (hypertension and obesity), hsa-mir-107 (obesity and T2DM), and hsa-mir-20^{a} (hypertension). Again, this factor is modifiable with improved metabolic control, and the risk of dementia can be delayed or even eliminated [64].

4. Aging and dementia

Dementia and especially Alzheimer's disease are more prevalent in aged population. However, not all patients are elderly. In addition, metabolic syndrome as early as adolescence can lead to early or elderly dementia.

One study, conducted on obese New York City minority (Hispanic, African-American) adolescents (average age 16) with and without metabolic syndrome, found that those with metabolic syndrome already showed reduced executive function and cognitive flexibility [65]. The authors suggest that even short-term metabolic alterations at that age would lead to neurological complications. Considering that at that age, white frontal matter is still in a developmental stage, these alterations will have serious effects in later life, leading to early development of dementia and Alzheimer' disease. Another study comparing healthy, obese, and type 2 diabetes adolescents found that both obese and diabetic adolescents (12–18 years) had reduction and alterations in both gray and white matter in the brain. Gray matter volumes in the right hippocampus were reduced in the obese and then diabetic groups [66]. Given these facts, and especially considering the current worldwide epidemics in both obesity and diabetes, interventions need to be initiated very early to avoid the heavy burden of dementia later in life.

It has also been noted that metabolic syndrome in early to middle adulthood causes a high risk of later dementia. Rosanna Tortelli et al. examined the cognitive status of Italian population compared with their metabolic status in a study conducted in 1985. They found that those with insulin resistance or diabetes in 1985 had an increased risk of suffering dementia 20 years later [67]. Chronic metabolic alterations have cardiovascular and believed to be cerebrovascular effects. These include damage to the small vessels in the brain. This leads to white matter damage (including amyloid lesions) and subsequently to dementia. However, it is interesting to note that metabolic syndrome increases the risk of dementia in patients <80 years old, but not older [68, 69]. Another published study, which followed women with metabolic syndrome for 12 years, found that metabolic syndrome increased the risk of dementia almost 2.5 times (OR = 2.47) [70]. Nevertheless, a review of the literature found inconclusive results, possibly due to the variety of definitions, criteria, and testing methods [71]. However, it has been suggested that the events related to metabolic syndrome that are manifested during middle age can develop independent pathways as time progresses, causing the appearance of diagnosable dementia later in life [10].

A study by Phrommintikul et al. [72] compared the factors associated with cognitive decline between younger (<65 years old) and elderly (≥65 years) patients with metabolic syndrome. They found that in the younger patients, most of the components of metabolic syndrome, in addition to fibroblast

Gene symbol	Location	Function	References
ApoE	19q13.2	The major cholesterol carrier in the brain	[54, 75]
CLU	8p21-p12	Important role in lipid transport in the brain	[76, 77]
ABCA	9p13.3	Regulate cholesterol homeostasis and transport of high-density lipoprotein cholesterol	[78, 79]
SOTL	9p13.3	Plays a key role in lipid metabolism and Aβ production	[80, 81]
CRI	1q32	Multifunctional mediator of innate immunity involved in amyloid (Aβ) clearance from brain	[82, 83]
PICALM	11q14	Regulator of brain Aβ production	[84]

Table 1.
Genes implicated in risk of metabolic syndrome and dementia.

growth factor 21 (FGF21), were important factors in cognitive decline. However, in the elderly patients, only BMI was a significant factor, indicating that the association between metabolic syndrome and dementia may also be age dependent. Nevertheless, the elderly may also have already suffered damage from the long-term effects of metabolic syndrome. The reasons for this age-dependent difference in the influence of metabolic syndrome remain unknown. On the other hand, a study of elderly Koreans found that metabolic syndrome and vitamin D deficiency were significant risk factors for dementia, increasing the risk threefold. This may be due to the fact that sufficient vitamin D has an anti-inflammatory and therefore protector effect [73]. Other studies exist, but the age cutoff has varied from 65 to 85 years. In all studies, nevertheless, those below the age cutoff showed an association between metabolic syndrome and Alzheimer's, while it had an inverse association in those over the cutoff point used [74]. This fact may also help explain the controversial results reported when trying to associate metabolic syndrome with dementia.

The genes implicated in obesity and metabolic syndrome increased the risk of developing AD in late life (**Table 1**).

5. Future and emerging trends

The presence of metabolic syndrome in early and middle adulthood is an important risk factor for developing Alzheimer's disease, as well as various other dementias. Physician's need to be aware of the importance of the presence of these components, not only as risk factors for dementia but also for their significant risk of cardiovascular disease. However, the various components of metabolic syndrome are each modifiable with changes in behavior and lifestyle. Physical activity and weight control are becoming points of emphasis in the attempt to prevent the progression of these diseases, as well as cardiovascular disease and all-cause and cardiovascular mortality.

In addition, some pharmacological treatments have been suggested for metabolic control and subsequent prevention of cardiovascular and dementia complications. These include anti-glucemiant medications, such as metformin, and antihypertensive and anti-inflammatory drugs, such as diuretics and nondihydropyridine calcium channel blocker.

Another emerging strategy involves the genetic risk of dementia. Research is searching for the genetic links between metabolic syndrome and dementia. Those with such genetic backgrounds should be monitored closely.

Finally, the mechanisms of dementia are still not entirely understood. Researchers are trying to unravel the mystery of the brain and its complex relationships, in order to better understand the best strategies to lower the prevalence of cardiovascular disease and to prevent the heartbreaking progression of dementia and especially of Alzheimer's disease.

6. Conclusion

In conclusion, it appears clear that the metabolic syndrome and its components increase the risk of developing Alzheimer's disease later in life. Most of these components are modifiable. In addition to the pharmacological treatments, such as the use of diuretics, lifestyle modifications can probably decrease the damage leading to Alzheimer's disease, as well as improving the quality of life of an increasingly older population. An added benefit would be the improvement in cardiovascular condition and the prevention and/or treatment of cardiovascular disease and cardiovascular mortality. Further research is needed to pursue three different avenues: (1) pathophysiology of the metabolic syndrome and dementia; (2) lifestyle interventions for the metabolic syndrome and their effect on the progression of dementia; and (3) the genetic link between the metabolic syndrome, AD, dementia progression, and cardiovascular disease.

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Chapter 4

Recovery Intervention to Promote Social Connectedness through Social Recreational Programs for Persons with Dementia: A Critical Analysis

Winnie Sun, Shelby-Lynne Clarke, Hanaan Madahey and Ping Zou

Abstract

People living with dementia and their caregivers continue to experience social isolation and are impacted by consequential negative health impacts. Social recreational programs are community-oriented programs that aim to reduce the levels of social isolation among persons with dementia and their informal caregivers by providing the opportunity to strengthen their social network through an increased social participation in the community. The purpose of this chapter is to focus on the reduction of social isolation experienced by persons living with dementia and their caregivers through the use of social recreational programs as a recovery intervention method. A review of the existing literature was conducted to explore the impact of social isolation among the dementia community and to explore the role of social recreational programs as an exemplar of recovery intervention to promote social connectedness. Literature was examined through thematic analysis to identify the emerging themes. Two main themes were examined through the literature review: (1) the impact of social isolation on the health and emotional burden experienced by the persons living with dementia and their caregivers; and (2) the therapeutic components of social recreational programs that represent as a potential recovery intervention to promote the sense of social inclusion. This chapter highlighted the need for future research to examine the effectiveness of social recreational programs in helping the persons with dementia and their caregivers to combat the negative effects of social isolation, as well as to empower them in actively participating and being socially engaged in the community.

Keywords: social isolation, social recreational program, recovery intervention, persons with dementia, informal caregiver

1. Introduction

On a global scale, more and more individuals are living longer, thus increasing the global aging population. It is important to take into consideration that as the

population ages, certain health requirements need to be fulfilled in order to meet the needs and specificity of care for older adults outside the traditional medical care model [1]. Such is the case among individuals living with dementia in addition to the family members and loved ones who care for them. It is crucial to be prepared as a society to address the needs of older adults at the community level and provide a more holistic approach to health and wellness. Although interest in dementia-friendly communities has received an increased attention over the past years, people living with dementia and their caregivers continue to be influenced by social isolation and experience the negative health consequences associated with it. For instance, social isolation has negative impacts on the health and well-being of persons with dementia, including loneliness and depression [1].

Social isolation is defined as an absence of social belongingness, feelings of loss relationships, or lack of meaningful interpersonal relationships [2]. The term can be mostly attributed to the lack of engagement with others, specifically in regards to the ability to make meaningful social relationships. Social isolation can manifest at an individual level as a lack of sense of belonging socially in a community, decline in social engagement, and having significantly minimal number of social contact, which contributes to a sense of inadequacy regarding satisfying quality relationships [2]. Social isolation as an individual's lack of sense of belonging socially in a community, decline in social engagement, and having significantly minimal social contact, which contributes to a sense of inadequacy regarding satisfying quality relationships [2]. Furthermore, it is important to highlight that the term social isolation can be categorized into two types: subjective and objective [3]. Subjective social isolation refers to the characteristics that result in shortage of companionship and social support, whereas objective social isolation is mainly due to lack of or infrequent social interactions, social network, or participation in social activities [3]. Therefore, social isolation can be attributed to an objective deprivation of social interactions and/or to subjective experience of social isolation and exclusion.

Numerous risk factors increase an older adult's probability of experiencing social isolation. Such factors that can influence an individual 's risk of social isolation include poor health, gender, loss of spouse, disabilities, living alone, place of residence, lack of transportation, as well as poverty and low confidence [4]. It is crucial to address that the aforementioned risk factors are just factors that increases an individual's likelihood of being socially isolated or excluded and that the factors do not imply a causal relationship to isolation. Many studies have outlined that the presence of more than one factor may influence the risk of social isolation. Social isolation has been shown to have negative health risks among older adults [5]. This is mainly due to the many losses occurring at the physical and psychological level, as well as changes in social roles, mobility, and living arrangements which can correlate with a decline in social relationships and an increase in isolation [5]. This is especially true for older adults with cognitive impairments, such as Alzheimer's or other forms of dementias as they can pose as a serious health risk. Not only does social isolation affect the individual living with dementia, but it can also be detrimental to the caregivers. This is mainly due to the increase in burden of care, facing obstacles, and balancing competing priorities (i.e. career and relationships) [6]. Some literature goes as far labelling caregivers as the "invisible second patients" due to the stressors that comes with caring for a person living with dementia, including fatigue and burnout [6].

To address the negative impacts associated with social isolation, social recreational programs have been developed to provide support systems to relieve the challenges faced by members in the dementia community [7]. The purpose of this chapter is to examine the effectiveness of social recreational programs as an exemplar of a recovery intervention for persons with dementia that focuses on reducing

the risk of social isolation associated with dementia. The objectives of this chapter are to provide an introduction to the medical overview of Alzheimer's disease and describe how dementia increases the risks of social isolation. In particular, this chapter will focus on examining the negative health implications of social isolation experienced by the persons living with dementia and their caregivers. The potential health benefits that social recreational programs provide to the clients, as well as the important role these programs play as a therapeutic component of illness recovery will be discussed. The critical analysis of the current literature regarding social recreational programs for persons living with dementia and their caregivers will help identify the existing gap in the literature, as well as providing implications and recommendations for future research directions.

2. Overview of Alzheimer's disease and social isolation

In the Statistics Canada 2016 report, it estimated that 35.6 million global citizens were living with dementia, and that the number is expected to double within the next 20 years [9]. When diagnosing an individual with dementia, physicians refer to the Diagnostic Manual of Mental Disorders (DSM) as a guide when determining whether the individual shows progressive tendencies of dementia [8]. The manual that is currently in practice is the DSM-5, which classifies dementia as a neurocognitive disorder. Generally, dementia is an umbrella term that encompasses a variety of symptoms related to the decline of cognitive function, which influences a person's ability to execute everyday activities [8]. In order to be diagnosed with dementia, one must meet certain criterions listed in the DSM-5 when determining major neurocognitive disorders such as: (a) showing evidence of significant mental decline that interferes with mundane daily routines; or (b) for milder cases show signs of modest cognitive decline with only little interference of daily active living [8]. The DSM-5 criteria for tendencies of dementia includes: (1) Cognitive changes, including new forgetfulness, difficulty finding words; (2) Psychiatric symptoms, such as withdrawal or apathy, depression, anxiety; (3) Personality changes, such as blunting and disinterest, social withdrawal; (4) Problem behaviors, such as wandering, agitation, restlessness; and (5) Changes in day-to-day functioning, including difficulty driving, getting lost, neglecting self-care, difficulty handling money [8].

There are different forms of dementia due to variances in the distinct expression of symptoms in addition to structural brain abnormalities. One of the most common forms of dementia is Alzheimer's disease, followed closely then by vascular dementia [9]. Other known types of dementia include dementia with Lewy bodies (DLB) and frontotemporal dementia. Moreover, impaired mental functions that arise due to the neurodegenerative disease include memory, language and communication, judgment and reasoning, and attention span [8]. Even emotional control and social behaviour and motivation are altered and may deteriorate as the disease progresses. Rates of dementia, including Alzheimer's disease and other forms of illness, are projected to increase continuously and double every 20 years [10]. It is estimated that in 2010, over 35 million people worldwide were living with dementia [11]. Dementia and Alzheimer's disease are considered as an abnormal process of aging. Common symptomology includes frequent memory loss and finding family members and friends unrecognizable [12]. It is believed that people first experience an asymptomatic period where neurodegenerative changes occur in the brain, while cognitive abilities remain stable. This preliminary phase occurs for a long duration and is followed by the progressive cognitive decline and the eventual, late-stage development of dementia [13].

People who develop dementia are at an increased risk for social isolation due to the natural process of aging, when cognitive and functional health may decline, where retirement may occur and result in a loss of social networks [14]. As individuals age, the risk for social isolation or exclusion increases. Aging with the development of dementia poses as an additional factor in increasing the risk of social isolation. Persons living with dementia report that their social circle decreases in size after friends learn of their diagnosis [15]. Caring for a person living with dementia is also a demanding task that can lead to social isolation. Informal caregiving is regarded as a rewarding task, however; it can have a negative impact on a caregiver's well-being and quality of life [16]. Social recreational programs are increasingly becoming an essential intervention that can help promote the engagement of persons with dementia and their caregivers in the participation of social activities and involvement in community services [17]. Positive health impacts are attributed to the meaningful socialization and community engagement through the participation in the social recreational programs.

3. The impact of social isolation associated with dementia

As the rates of dementia and Alzheimer's disease continue to increase globally, it is vital to examine the negative health impacts that the illness has on persons living with dementia and their social network. Meanwhile there is evidence of an increase in caregiver burden and distress while providing assistance to their loved ones living with dementia. The following section explores the health and emotional burden of persons with dementia and the associated impact on their informal caregiver's health and well-being.

3.1 The health and emotional burden of persons with dementia

Physical and mental health symptoms as a result of social isolation and the diagnosis of Alzheimer's disease can be a great burden upon the persons living with dementia. El Haj et al. [14] discussed the impact of social isolation and its associated emotional impact such as loneliness that affects the individuals with Alzheimer's disease. The researchers indicated that these isolating experiences may result in hallucinogenic health issues. For instance, the person living with dementia may develop the hallucinations as a result of boredom and use them as an escape method from the feelings of loneliness and social isolation [14]. This study revealed that Alzheimer's disease has a great impact on the levels of loneliness and social isolation of persons with dementia compared to the participants in a healthy control group. The research findings suggested that the hallucinations experienced by the study participants were a result of increased social isolation in the lives of the persons living with dementia. This study provided significant insight into the specific health and emotional consequences associated with the increase in an individual's level of social isolation among the dementia populations.

Other researchers emphasized the impact of dementia on a person's social interactions through examining cognitive impairments and how an individual may be excluded from social resources, such as interactions with family and friends leading to the development of loneliness and depression [18]. Examining how dementia and cognitive decline can result in poor social interactions is the key to an increased understanding of how chronic physical and mental health conditions can arise. This understanding can allow for the development of preventative measures for the purpose of lessening the impact of the illness on one's social interactions, as well as a person's physical and mental health. The findings of this study concluded that

dementia has a significant influence on social resources, such as relationships with family and friends. This can contribute to social isolation of a person living with dementia and therefore provides the ground for the development of chronic health conditions. This study suggested that the causes of loneliness and social isolation in persons with dementia are inter-related, and new research is needed to provide information to the future development of intervention programs that address the barriers associated with the multifactorial causes [18].

Persons with dementia who are diagnosed with depression are particularly vulnerable for the development of social isolation. Shub et al. [19] examined the levels of irritability and social isolation in war veterans of whom have been diagnosed with Alzheimer's disease. The study recruited a group of participants who had an accompanying clinical diagnosis of depression, and another group of participants who only had Alzheimer's disease. The study findings suggested that a person living with dementia who was additionally diagnosed with depression tend to have a greater increase in social isolation levels compared to the other participants who did not have depression [19]. It is important to assess the additional strain a mental health condition can put on persons living with dementia and how it impacts their feelings of social connectedness. As social isolation is a major risk associated with dementia, it is important for the researchers to critically analyze its implications on the health and well-being of the individuals with cognitive impairment. Previous research studies concluded that persons with dementia were more likely to experience social isolation which may be accompanied by mental and physical health conditions [17–19]. Burholt et al. [18] underscored the importance of recognizing the interrelationship between cognitive and mental health status and how the impairment in one domain can negatively impact the other. These research studies highlighted the prevalence of social isolation among persons with dementia and provided evidence to demonstrate the health consequences an individual may suffer from who is experiencing a cognitive impairment such as dementia and Alzheimer's disease. These negative health impacts can include loneliness, depression and other physical or mental health conditions.

3.2 The health and emotional burden of informal caregivers

Bass et al. [20] examined the extent of the caregiving burden among the caregivers of the veterans living with dementia. This study is crucial for the understanding of how certain health effects can present themselves due to the negative experiences that occurred while caring for a loved one with dementia. Study findings revealed that the caregivers for persons with dementia experienced a high level of social isolation, which can lead to depressive symptoms, emotional strain and unmet needs [20]. These health conditions were attributed to the person with dementia's level of cognitive impairment, behavioral tendencies and their increased need for care and support. An additional predictive factor of caregiver burden was the additional health care conditions that the person with dementia is experiencing [20]. As a result of the emotional burden, caregivers can experience high levels of stress which may further lead to the development of health issues. This study provided significant insight into the negative effects of social isolation that equally affect both the persons with dementia, and their informal caregivers. **Figure 1** demonstrates the process of how negative health issues develop and impact the caregiver as a result of caring for a person living with dementia. The risk for the development of health issues begins at diagnosis and is fueled by the experiences of social isolation.

Since social isolation is found to be a risk factor for the caregivers of persons with cognitive impairment, it may act as a potential barrier for the caregivers to be connected with the appropriate community support programs that might benefit

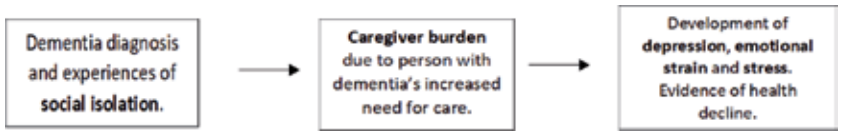

Figure 1.
The trajectory of how social isolation negatively impacts the caregivers of persons with dementia.

themselves and their loved ones. Researchers analyzed the effectiveness of a linking system designed to connect caregivers to local support programs soon after their loved one has been diagnosed with dementia [21]. Caregivers may be delayed in finding the appropriate community support programs because of their personal beliefs and values or they simply lack the necessary knowledge of the availability of these support programs within the community. The linking system developed in the study allowed for establishing connections between informal caregivers, health care professionals and community programs and resources [21]. This research study provided insight into the development of an effective method to connect caregivers to the community support programs after the dementia diagnosis of their loved ones. Referrals and linking strategies can help support both health care professionals and their caregivers in effectively managing dementia and thereby may reduce the associated caregiver burden [21]. These research studies highlighted the role of social recreational programs in the community for persons living with dementia and their caregivers with the goal of improving their sense of social connectedness and reducing the risk for health and emotional burden associated with the illness.

4. The role of social recreational programs as a recovery intervention

Social recreational programs are developed to provide individual impacted by dementia with the appropriate community support programs and public education services. These services aim at reducing the stigma associated with dementia and increasing the levels of social inclusion among people living with dementia and their caregivers [22]. Social recreational program should be regarded as an important component of the recovery intervention for persons with dementia. The effectiveness of social recreational programs and the associated health benefits provided to the individuals with dementia are discussed in this section.

As the number of older adults in society increases, it presents many unique and complex health needs that may not be met through the conventional health care model. Many within the field of gerontology are recognizing this concept and the significance of meaningful social interactions and support to improve overall quality of life and well-being. A research study examined whether the Community-Engaged Arts (CEA) programs developed in Vancouver, Canada by the Arts, Health and Seniors (AHS) Program addressed the question of how implementing more inclusive and supportive communities can support older citizens achieve and improve overall quality of life [1]. There were gaps found within the literature as implementing social inclusion programs for seniors was relatively new, with few anecdotal evidences and limited academic research conducted surrounding the topic [1]. The researchers conducted a qualitative study analyzing how the AHS program addressed the older adult's experience with community involvement using methodologies such as participant observation, informal interviews, and review of documents [1]. Findings from the study concluded that the AHS program supported social networks for the older adults to increase their participation within the community [1]. Participants of the AHS program from all four different neighborhoods

that were offered the intervention expressed that engaging with young people by making art together through an intergenerational approach provided a sense of belonging within a community through mutual appreciation of the arts and allowed the co-creation of meaningful connections [1].

Another research study took a similar approach concerning community-based arts programs for persons living with dementia and their caregivers by evaluating its potential in creating social and cognitive engagement between both groups [23]. Participants of the study included 13 persons living with dementia and 21 caregivers who were involved in the gallery tours and art classes at the Frye Art Museum in Seattle, Washington [23]. The research employed a qualitative approach using semi-structured interviews in which the data were analyzed to generate common themes regarding the participant's experiences with the programs. Among the persons living with dementia, themes such as mindfulness, enjoyment, engagement, socialization, and personhood were some of the major themes emerged from the study [23]. The study highlighted the importance of future funding to support the development of this type of art programs as these programs were found to be effective in increasing social connectedness among the persons with dementia.

Additional studies have implemented art-based interventions for persons with dementia and their caregivers with the aim of increasing social connectedness and reducing caregiver burden and distress. For instance, a research study provided persons living with dementia and their caregivers with an intervention program based in an art gallery where findings suggested a greater level of social interaction among study participants, feelings of social inclusion and improved quality of life for the persons living with dementia [24]. A different study examined an art-based therapy program for persons with dementia. The study findings supported the implementation of art-based therapy programs for fostering social connections with other program participants, as well as the opportunities to connect the individuals with the appropriate programs and services provided in the community [1]. One study also explored the caregiver's perspective while analyzing the effectiveness of an art-based program for persons with dementia [25]. The results indicated that caregivers experienced more meaningful interactions with the person with dementia and the program provided them with an opportunity for stress relief and increased sense of social acceptance [25]. Art-based therapy interventions for persons with dementia and their caregivers can potentially be an effective recovery intervention that contributes to the positive health benefits and the development of social inclusion in the community.

Other intervention programs such as the community-based walking program was assessed in the literature review. One randomized controlled trial about a walking program is through Takasaki Project which took place in three different locations in Japan [26]. The purpose of the research was to evaluate the effectiveness of a community-based program for the prevention of further deterioration of cognitive impairment of older adults through walking exercises. The program allowed and encouraged participants to improve walking routines through a gradual process in a group environment, thus providing the combined advantages of exercising and social interactions to take place [26]. The results obtained from the qualitative research indicated that the walking program resulted in increased motivation, positive attitudes, as well as increased social connectedness [26]. Before initiation or participation in the project, participants felt alienated from the society due to changes occurred in their social roles, and having felt some form of emotional isolation, which consequently posed a risk to a decline in their mental status [26]. However, after the implementation of the walking program presented in the Tasaki Project, participants expressed the increased sense of community belonging through the intervention.

The influence of social stigma may result in an increase of social isolation among persons living with dementia and their caregivers. Harris and Caporella [27] explored the stigma associated with dementia and studied the effectiveness of a choir program designed for university students, persons with dementia and their caregivers in an effort to reduce the stigma and increase social interaction among the study participants. Findings from this study concluded that the choir program increased the levels of social connectedness between the students and the dementia couples, while the social stigma associated with the illness decreased from the perspectives of the students. The social interactions between the dementia couples also increased as a result of the choir program [27]. The study findings indicated that persons living with dementia and their caregivers may be more vulnerable to societal stigmas associated with the disease, which in turn would increase their risk for social isolation. Particularly, university students and the general public may not be well-educated about Alzheimer's disease and can develop misunderstanding towards the dementia populations as a whole. This study highlighted the impact of societal influences have on the levels of social isolation or exclusion of persons with dementia and their caregivers. The study proposed that the development of social recreational programs can potentially become an effective intervention to promote the successful recovery from the negative impact of social isolation.

Using a narrative approach, a research study explored the journey of the illness trajectory that the persons with dementia and their caregivers have experienced [28]. The narrative experiences began at a time prior to the participation in a social recreational program that were aimed at increasing the social interactions of the study participants. These narratives were completed with the descriptions of how the persons with dementia and their caregiver benefitted from the social recreational program based on their perspectives [28]. This methodology offered the researchers with an in-depth insight into the lived experiences of persons with dementia, as well as their interpreted meaning about the essence of social inclusion [28]. For instance, this study found that after the participation in the social recreational program, study participants expressed an increased social connection with others who were experiencing the same illness, and this sense of mutuality was therapeutic to them as it helped promote a feeling of comfort and acceptance from others [28]. The critical analysis of the above research studies highlighted the therapeutic impact of social recreational program as an exemplar of an effective recovery approach that helps promote the social participation and inclusion of persons with dementia in the community.

5. Establishing social connectedness between persons with dementia and their caregivers

As discussed in the review of the literature, community-based programs with the aim of promoting social connectedness can be implemented to reduce the health and emotional burden of the illness on both the persons with dementia and their caregivers. These programs were found to allow for the development of positive social interactions with others, and an increased sense of acceptance and well-being, which are attributed to be an effective approach to support illness recovery, as well as reducing the risk of additional chronic health conditions, such as depression [20]. In addition to the increased sense of social connectedness, researchers who evaluated the effectiveness of social recreational program indicated that the community-oriented programs can help promote an increased awareness and understanding of dementia through the delivery of educational training [29]. Roberts and Silverio [30] conducted a study that focused on evaluating the

effectiveness of social recreational program for people living with early-stage Alzheimer's disease and their caregivers. The results indicated that the study participants expressed an increased knowledge and understanding of their illness experience as a result of the educational training about their illness trajectory of Alzheimer's disease. The study participants indicated that the increased knowledge and understanding of their illness helped empower them in strengthening their social network and resources in the community. Social recreational programs are crucial for maintaining a person with dementia and their caregiver's social networks and interactions, and they are beneficial in reducing the effects of social isolation as a result of the disease process [14].

It is essential to take into account the health and well-being of the caregiver as they play a crucial role in the health care services provided for the older adult with dementia. The study that examined the use of museum-based programs catered to both dyads showed benefits for both persons with dementia and caregivers who participated in the arts program [23]. Results obtained from the study through in-depth interviews revealed common themes that arose among participants such as engagement, mindfulness, socialization, joint respite, as well as relationship themes including normalization, affirmation, and relationship growth [23]. The program provided a means of social interactions among participants of the arts programs through discussions of artistic creations and partaking in hands-on artwork as it allowed a means of expression and personal exploration [23]. The increased socialization associated with the program was identified as a major theme among the study participants. The art-based interventions allowed the persons with dementia to engage in reminiscence of experiences and relationship affirmation, which in turn, elevated social connectedness among members of the program [23].

As caregivers, many challenges can arise where caregivers of persons living with dementia are often referred to as "second victims of dementia" [31]. The caregiving workload resulted in a heavy burden upon the caregivers that included physical, emotional, financial, as well as social problems [31]. A research study was conducted with the aim of improving the health and quality of life of caregivers with individuals of Alzheimer's disease by providing treatment that focused on four main components: (1) counseling sessions tailored for each caregiver; (2) family-centered counseling sessions; (3) encouraging participation in community support groups; and (4) continuous availability of counselors to provide follow-up telephone contact [32]. Findings from the study indicated that psychosocial interventions which emphasized social support, led to significant improvements in the health of the caregivers. These results are interesting, as the intervention did not emphasize any health promotion, exercise, or vaccination to cause such improvements in health to occur. This study underscored the importance of counseling and social support interventions for caregivers of persons with Alzheimer disease as it provided a means of preserving health and quality of life among vulnerable dementia carers who were at risk for health decline [23]. Providing social support and recreational activities involving both persons with dementia and their caregivers can support the long-term development of relationship roles and responsibilities; facilitate open communication; and enable the caregivers to develop a sense of partnership that will promote the feelings of enjoyment and togetherness while providing caregiving [33]. **Table 1** provides the examples of stimulating programs developed by Alzheimer's Society of Canada that are effective for persons with dementia and their caregivers to promote their sense of social connectedness through active participation of social recreational activities in the community [35].

Arts/Choir Program	Persons with dementia who enjoy music and singing are encouraged to join the choral group. Singing can elicit pleasant memories from past experiences, release endorphins and help decrease anxiety and depression.
Brain Wave Cafe	Brain Wave Cafés offer a dementia friendly place for persons with dementia, their family and friends to meet for stimulating conversation, support and engaging activities. Social interaction contributes to a greater sense of well-being, promote mental function and a sense of connectedness.
Walking Buddies	This outdoor walking program session at various walking trails in the local community. Volunteers accompany persons with dementia at their respective fitness levels make it accessible for all.
Minds-in-Motion	Minds in Motion is a community-based social program that incorporates physical activity and mental stimulation for people with early to mid-stage signs dementia and their care partners.
IPOD Project	Living with dementia can trigger a range of emotional responses which may seem out of character for an individual. One of the things to alleviate these feelings is offer personalized music. There is a growing body of evidence showing that music can be used to help connect with and engage a person with dementia. Through consultation with the person with dementia and/or their caregiver, a personalized playlist is created and loaded onto an iPod shuffle. Music and Memory iPod project aims to provide the means and opportunity for a person with dementia to experience the benefits of listening to well loved, meaningful music.

Table 1.
Examples of social recreational programs by Alzheimer's Society of Canada.

6. Future and emerging research trends

This chapter examined the impact of social isolation on persons living with dementia and their caregivers. Researchers found that the risk for social isolation increases with age, and older people with dementia are particularly more vulnerable for developing loneliness and depression as a result of social isolation [16]. For instance, researchers have examined the negative emotional impact, such as loneliness as a result of the levels of social isolation in the lives of the persons with dementia and their carers [14, 18]. Studies also focused on examining the increased risk for caregiver burden and distress associated with the care of persons with dementia who have the additional diagnosis of depression [19]. Particularly, a lack of education about the availability of community resources and an increased responsibility of care for a loved one with dementia can lead to a greater risk for the development of physical and mental health conditions in caregivers [12, 13].

Alzheimer's disease will impact a greater portion of the population in the coming years. This presents a greater risk for persons living with dementia and their caregivers feeling isolated from the social aspects of their lives as a result of the disease. Future research should continue to explore areas of emotional burden or strain for both the persons living with dementia and their caregivers and what interventions are beneficial to their well being. Current research suggests that stigma increases the likelihood of social isolation among people with dementia and their caregivers by acting as barriers to the utilization of available services that will reduce their health burdens associated with the disease. [34] Research findings indicated that the risk for social isolation increases with age, and older people with dementia are particularly more vulnerable at developing loneliness and depression as a result of social isolation [5]. This can be associated with the social stigma surrounding Alzheimer's disease and dementia, as well as the implications of stereotypes associated with ageism.

Current studies demonstrated the importance of social recreational programs in promoting a sense of social connectedness for persons with dementia and their caregivers. These included strategies such as choir programs, art-based therapies, narrative approaches and educational training. These programs are exemplars of potential recovery interventions targeted at supporting persons with dementia to develop a greater sense of social connectedness in the community, as well as promoting their recovery from the negative health and emotional impact associated with their cognitive impairment. The lack of education about the availability of community resources and an increased responsibility of care for a loved one with dementia can lead to a greater risk for the development of physical and mental health conditions [11, 12]. Future research should continue to focus specifically on the knowledge of caregivers and persons living with dementia regarding the benefits and appropriate utilization of social recreational programs. The causes of loneliness and social isolation in persons with dementia are inter-related, and new research is needed to provide information to the future development of intervention programs that address the barriers associated with the multifactorial causes [18]. There is an urgent need for more research regarding the effectiveness of social recreational programs in supporting the persons with dementia and their caregivers, as well as raising awareness about these programs and services to combat the negative effects of social isolation.

7. Conclusion

The critical analysis of the literature highlighted the need for more research regarding the effectiveness of social recreational programs in helping the persons with dementia and their caregivers to combat the negative effects of social isolation. Social inclusion can provide persons living with dementia many positive physical and mental health benefits, including building meaningful relationships and social connections, as well as reducing the societal stigma associated with Alzheimer's disease. Public education of Alzheimer's disease and dementia can help reduce the current stigma surrounding the disease. Educating the dementia communities of services available to them is also an important factor in decreasing the social isolation experienced by persons living with dementia and their caregivers. Through reducing social isolation, health care professionals can support the persons with dementia into the road of recovery with the goal of enabling them to feel empowered in actively participating and being socially engaged in the community.

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Advances in Dementia Research provides a comprehensive overview of Alzheimer's dementia. This book also represents the association between the components of metabolic syndrome and Alzheimer's disease. Vascular dementia associated with neurodegeneration and cognitive impairments is due to multiple complications of the neurovascular system. This book attempts to explore the recent advancements of enzyme targets for the management of vascular dementia. Furthermore, this book highlights the effectiveness of social recreational programs as an example of a recovery intervention for persons with dementia that focuses on reducing the risk of social isolation associated with dementia. Together the insightful research presented in this book provides valuable information for neuroscientists, researchers, medical professionals, academicians, and upper-level students, as well as for industry professionals.

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