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Perspective Chapter: Exercise-Eating Pattern and Social Inclusion (EES) is an Effective Modulator of Pathophysiological Hallmarks of Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD), a common type of dementia, characterized by the presence of aggregated extracellular amyloid-beta ($A\beta$), intracellular hyper phosphorylation of tau protein and neurodegenerative with cognitive decline. It is projected that 141 million people will be suffering with AD by 2050 but no effective drug treatment is discovered without side effects. There is an urgent need for the application of alternative and non-pharmacological interventions for AD. Sporadically found that exercise or diet therapy or social activity may positively influence the AD. In this review we discussed the process of how Exercise-Eating pattern and Social inclusion (EES) has been shown to have fewer side effects and better adherence with AD. In this mechanism the EES can modulate the brain metabolic factors, brain-derived neurotrophic, ketone bodies, lactate, cathepsin-B, irisin, hormonal balance in AD. This review also described the potential biological mechanisms underlying exercise (modulation of biomolecule turnover, antioxidant and anti inflammation), eating pattern (bioactive compounds) and social inclusion that is very important to ameliorate the pathophysiological hallmarks of Alzheimer's disease. Thus, this EES can be an effective approach to manage the neurodegenerative disorder as well as Alzheimer's disease.

Keywords: Exercise-eating pattern and social inclusion (EES), neuromodulators, metabolic factors, pathophysiological-hallmarks, new approach to AD

1. Introduction

Alzheimer's disease (AD) is a form of dementia, currently affecting over 55 million people worldwide. This alarming situation is projected to the elevation of 88 million people by 2050 [1, 2]. It is a complex mechanism of neurodegenerative disorder clinically categorized by advanced and continuing deterioration in intellectual capability of the brain and biochemical change due to the presence of neurotic threads, specific areas of the brain function damage subsequently synaptic signal loss. This consequence occurs due to the accumulation of specific protein amyloid- β to the external neurons and modification of the specific tau protein by hyper phosphorylation and ultimately

neurofibrillary tangles (NFTs) are formed in the neuron cell of the brain. This mechanism is responsible to intellectual deficit, remembrance loss, and then neuron expiry [3, 4]. AD is one of the pathetic disease eases due to the presence of disability in the oldest people and it was found that the prevalence of AD is less than 1% in the people who are underneath 60 years of age, but this prevalence is increasing to 40% among people who are older than 85 [5]. The most important thing is that, there is no specific drug for the treatment of AD to date [4]. The alarming disease burden is concerned in the world, because the projected global population of older adults (defined as those aged >60 year) in the year of 2050 will be 2 billion (approximately 21% of the world's population) out of them 392 million will be over 80 years of old [6]. Presently preventive measures are getting more attention than pharmacological interventions after unsuccessful clinical trials of some promising drugs designed for targeting A β and tau proteins. Though, there is no specific treatment of the AD but world scientists are trying to control the gradual growth of AD by multidomain non pharmaceutical intervention such as exercise or diet, and intellectual or physical activity that can prevent cognitive decline at-risk of the oldest population [7]. There is no available information about together-intervention of exercise with diet pattern and social inclusion to ameliorate the prevalence of AD. This is a very important and socially demanding strategy of mass elder people rather than pharmacological intervention.

2. Pathological hallmarks of AD

Two most important determinants in or out of the neuron cells in the brain that are involved in the mechanism of dementia progression, i.e., the β -amyloid peptide and tau proteins. The pathophysiological change of AD is normally carried out by measuring the deposition of β -amyloid peptide, a 39–43 amino acid chain that is produced in the brain and organized a flame-shaped neurofibrillary tangles of tau protein in the affected region of the brain [3]. In patient of AD, one of the determinant (β -amyloid peptide) in the brain is found abnormal due to the genetic mutations in the gene of precursor protein of β -amyloid peptide and Presenilins (PS1 and PS2) which lead to anomalous A β accumulation outside the neuron in the brain [4]. Another important determinant tau protein treats the microtubule gathering and maintenance due to the hyperphosphorylation of tau protein and is the cause of AD pathology, The actually mechanism of abnormal microtubule gathering is hyper phosphorylation of tau protein because the modified tau protein can accelerate the formation of neurofibrillary tangles (NFTs), that is associated with loss of remembrance and wisdom hearts [8]. The microtubule disassembly (neurofibrillary tangles; NFTs) may likewise found in other distinctive neurodegenerative diseases, have some distinguishing morphological change rather than AD and this is due to a distinctive conformation of tau isoforms that could easily differentiate from AD [9]. On the other hand, the degree of dementia was observed to be weakly correlated with the amounts and distribution of A β deposition within the brain [10]. In particular, the increased deposition of A β peptide outside the neuron cell can cause abnormal synaptic signal transduction, intellectual linkage, mitochondrial energy transduction, apoptosis of neuronal cell and, ultimately remembrance forfeiture, the hallmark of AD [11, 12]. Even though some neurotoxicity occurs in the neuronal cell, the mechanism of neurotoxicity caused by A β is not fully discovered. Although some studies showed that the abnormal accumulation of A β peptide in the brain causes induction of oxidative stress and neuroinflammation, the most important cause of neurotoxicity [13]. Early detection of the determinants is one the most important parameters for the management of AD. But the aforementioned two determinants are very difficult to early determination. Thus defective metabolism of glucose in the brain may be

Figure 1.
Various modifiable risk determinants in AD pathology [4].

one of the earliest hallmarks of AD. The detection of brain glucose hypometabolism is measured by the determination of fluoro-2-deoxy-D-glucose positron emission tomography imaging system. This technique has been suggested as an effective early diagnostic tool for AD. Several studies showed the sensitivity and effectiveness of the brain glucose hypometabolism technique (about 90%) for the early diagnosis of AD [14]. Moreover, amino acids may be another hallmark of AD. For instance, abnormal elevation of homocysteine (Hcy) in the AD population. Studies showed that hyperhomocysteinemia is accompanied with amplified intellectual deterioration in healthy older adults with a higher risk of perceptive deficiency [15]. Another study found that abnormal plasma homocysteine and distressed homocysteine amino acid metabolism are risk factors for intellectual concept [5]. Several potential mechanisms have been studied on the harmful effects of homocysteine amino acid in the brain including oxidative deterioration [16], cerebrovascular impairment [17], DNA destruction [18], and activation of N-methyl-D-aspartate receptors [19]. In the **Figure 1**, we summarized the various modifiable risk determinants that are responsible for AD pathology.

3. Mechanisms involved for the development of AD

The A β peptide (approximate size ~4 kDa) is resulting by cleavage of the larger β -amyloid precursor protein (A β PP). β - and γ -secretase are the two membrane-bound endoprotease activities sequentially cleaved the A β PP to produce (**Figure 2**) the most abundant fragment A β 40 (~80 to 90%) and A β 42 (~5 to 10%). The somewhat extensive forms of A β , predominantly A β 42, is the principal culprit for the deposition in the brain [20]. The enzyme, β -Secretase is a protease which have two major homologous (>65%) forms, one is β -site Amyloid Precursor Protein Cleaving Enzyme (BACE1) and the other is BACE2. The most important Enzyme BACE1

is mainly accountable for β -amyloid peptide production higher in the brain than BACE2 which is mostly present in the peripheral tissues. Animal studies stated that the protease BACE1 is the foremost β -secretase action in the brain, however, some residual motion might be attributable by the BACE2. Besides the brain, The BACE1 are also found in another cell type such as pancreatic β -cells where they are highly expressed in mRNA levels, however, this pancreatic isoform of BACE1 is distinctive from the brain and may not cleave A β PP. It was found that BACE1 action upsurges with oldness and is highly found (two to five-fold) in irregular AD [21, 22]. It is important that the lack of protease activity of BACE1 is related to prevent β -amyloid peptide synthesis [23]. Recent studies also observed that in a suitable situation cathepsin B or cathepsin D may help to serve such kind of enzyme like β -secretase enzymes. The two enzymes, β - and γ -secretase were considered to be the leading goals for the advance of anti-AD medications [24]. For example, alterations in γ -secretase activity by the change of allosteric γ -secretase controlling representatives may prevent the production of β -amyloid peptide [25]. Study showed a reduction in BACE1 expression that is related to glucose metabolism via regulation of insulin mRNA expression. In vivo experiments stated that reduction of BACE1 expression may lower plasma insulin concentrations and body weight through the controlling of regular glucose acceptance and insulin sensitivity [26].

Another relationship of AD has also been exposed to be concomitant with inflammation, glucose metabolism and hormonal balance. For instance, the inflammatory markers have been isolated in the cerebrospinal fluid (CSF) and abnormal amyloid formation found in the brain of AD that is much related to high expression of inflammatory molecules interleukin-6 (IL-6). This relationship is not only found in the brain but also in the other fluid such as the lumbar and ventricular region in patients with AD. Another relationship was found that circulating IL-6 is highly expressed before symptomatic sign of dementia and this increased IL-6 is related with low male hormone like testosterone in older men with type-II diabetes Mellitus (T2DM) and AD [27–29]. It was found that male hormone secretion is hampered by inflammatory molecules IL-6 and this is much

Figure 2.
Amyloidogenic pathway involved for development of AD [32–35].

related to inflammation and oxidative stress, hormonal imbalance and T2DM with AD pathology [30–31]. **Figure 2** summarized the amyloidogenic pathway involved for development of AD [32–35].

4. Mechanisms involved for the prevention of AD

The prevention of AD means the degradation of β -amyloid peptides by enzymes such as A β degrading enzyme Neprilysin (NEP) and insulin degrading enzyme (IDE). There are many enzymes, the aforementioned two important enzymes are metallo-protease which are responsible for most of the A β degradation [36, 37]. The membrane bound Neprilysin is actually type II metalloprotease which degrades the extracellular variety of peptides but the IDE enzyme can degrade both intra- and extracellular [38]. Though the affinity of IDE enzyme to the insulin is (twenty times higher) higher than A β but it hydrolyzes slowly. It is important that the insulin may be responsible for cleavage of β -amyloid peptides, this is the basic mechanism among type II diabetes, hyperinsulinemia, and AD [39, 40]. Most of the A β degradation occurs by the influence of NEP, like lysosomal degradation of cathepsin B [41]. Another study stated that other enzymes such as Endothelin Converting Enzyme (ECE), Angiotensin-Converting Enzyme (ACE), and Matrix Metalloproteinase-9 (MMP-9) may also have A β degrading properties [42]. Though the substantial degradation of β -amyloid peptides occurs in the brain, their undegraded portion is transported through the blood brain barrier (BBB) into the circulation by specific mechanisms. The soluble part of β -amyloid peptide is switched through the BBB into the abluminal site of the brain by the low-density lipoprotein receptor-related protein (LRP) and into the luminal side of the blood by the receptor for advanced glycation end products (RAGE) [43, 44]. Disturbing this mechanism may cause an increase of A β level which may be attached with other widespread co-morbid vascular irregularities in the brain function of AD. This change may exaggerate the development of amyloid pathology [45]. **Figure 3** summarized the detailed preventive mechanism of AD by A β degradation pathway. The frequency of AD is found meaningfully higher in women than to men (almost two-thirds) indicating a strong association of sex hormones with the AD [46]. Study observed that testosterone levels are inversely associated with the plasma levels of β -amyloid peptides in elderly men population [47]. Testosterone may provide different neuroprotective effects including enlightening intellectual presentation and synaptic signal transduction by increasing relaxation, modulation synapse density level on the brain hippocampal dendritic spines [48, 49]. This hormone is also important for maintaining hippocampal function in elderly population [50], increasing blood supply to the cerebral and increasing glucose metabolism in the responsive brain regions as well as reduced the aggregation of β -amyloid peptides and neurotoxicity. Testosterone may reducing the tau protein hyperphosphorylation and in vivo experiment showed that the reduction of testosterone is directly associated with reduce intellectual performance, and it could be revised by testosterone supplementation [51, 52]. Women are more prone to AD than men because testosterone is basically a male hormone and most abundant testosterone is converted into estrogen and other adrenal hormones in women. The study showed that women are more prone to AD symptoms due to lack of testosterone [53]. Previous animal study indicated that testosterone (in male) and estrogen (in female) could modulate the invention of β -amyloid peptides by the disturbing of BACE1 action [54, 55]. The hormone like testosterone is an effective modulator of endogenous β -amyloid peptides degrading enzymes such as NEP. Animal study observed that neuronal expression of NEP is enhanced by the action of testosterone which in turn reduces the β -amyloid peptide level and ultimately reduces the symptoms of AD [56]. The increase of β -amyloid peptides degrading enzymes positively

Figure 3.
Preventive mechanism of AD by Aβ degradation pathway.

influence on the level of toxicity or fibrillization of amylin [57, 58]. Testosterone may regulate the enzymes NEP and IDE and improve the AD conditions [53]. Another protein, the APOE ε4 allele is very related to the AD, promoting β-amyloid peptides clearance, and it was found that the isoform ApoE ε2 and ApoE ε3 are very efficient than the ApoE ε4 protein. The modification among the isoform may influence the ability of ApoE to promote β-amyloid peptides degradation, and the modification of ApoE is subjected by its lipid carrier molecule ABCA1, whereby higher modification may increases the clearance of β-amyloid peptides [59, 60]. The insulin impairment and the brain function are associated with AD [53]. Brain insulin is very special and mostly originated from endogenous production which is not influenced by the plasma insulin [61]. The mechanism of insulin action in the brain describes the signal transduction via signal cascade pathway. In which first insulin binds to the insulin receptors and then phosphorylation occurs on multiple substrates such as insulin receptor substrate-1 and insulin receptor substrate-II. This phosphorylated substrate activates the downstream signaling pathways and activates the phosphatidylinositol 3-kinase, which is an important modulator for synaptic malleability, education, and remembrance. The activation of phosphatidylinositol 3-kinase subsequently activates Akt which phosphorylates enzymes related to glucose metabolism such as glycogen synthase kinase (GSK) 3β. Then GSK3β regulates tau protein phosphorylation in AD, and thereby leading to neurofibrillary tangle formation [62, 63]. In vitro and in vivo studies demonstrated that impairment of insulin signaling pathway is associated with the AD pathology [64–66]. There is a strong linkage among the hormone testosterone, insulin and glucose metabolism through glucose transporter and insulin receptor protein [67]. Studies have shown that testosterone influence the glucose uptake and transporter via activation of liver kinase B1/AMP-activated protein kinase signaling pathway in fat cell, where AMPK plays an important role for decreasing mTOR signaling activity and promotes lysosomal degradation of β-amyloid peptides in AD. However, this mechanism can also lead to β-amyloid peptides generation and tau phosphorylation [68, 69]. Several studies have shown that both precursor protein (APP) and β-amyloid peptides co-localize

in mitochondria, suggesting the possibility of mitochondrial function is associated with APP biology [70]. Ketone bodies may block the mitochondrial amyloid entry and improve understanding capability [71]. This ability would predictably ameliorate A β -mediated suppression of respiratory chain function and perhaps could rescue the bioenergetics hypo metabolism that is observed in AD brains [72]. Alternatively, improving mitochondrial performance outright could reduce the production of A β and increase the production of soluble APP α [73].

5. Dietary pattern for the prevention and treatment of Alzheimer disease

Dietary patterns which are rich in antioxidant and anti-inflammatory properties, may involve the establishment of auspicious attitudes in the treatment of intellectual deterioration or suspending the development of dementia in the brain [74]. The bio ingredient of diet can change the epigenetic by regulating deoxyribonucleic acid (DNA) modification such as methylation, acetylation, histone protein modifications, and changes of gene expression in the ribonucleic acid (RNA) level. The epigenetic modification may influence the expression of particular genes and subsequently particular marker molecules that are responsible for epigenetic alterations [75]. Lipidation of several molecules are important for brain function, one of them are polyunsaturated fatty acids (PUFAs) [76]. The PUFA are the important component of neuronal cell membranes, which is responsible for membrane fluidity. The crossing of molecules through the membrane allows them for cell signaling and neuronal protection [77]. The essential PUFAs play not only neuroprotection but also involve development and brain functions. They also have antioxidant, anti-excitotoxic, and anti-inflammatory activities in the brain. Imbalance of PUFA has been found in neuropsychiatric health including dementia. The beneficial effects of long-chain omega-3 PUFAs have been observed in populations where long-chain omega-3 PUFAs effectively reduce the risk of cerebral damage in individuals without dementia. This is supported by other studies in such a way that omega-3 fatty acid may effectively reduce the initial stages of intellectual deterioration [78]. Another dietary bioactive compound, curcumin (turmeric powder), plays an important role against β -amyloid peptides deposition in the AD because they have potent antioxidant, anti-inflammatory, and neuroprotective function [79]. The bioactive compound, curcumin, regulates the genetic control by down regulation of several gene expression such as class I HDACs (HDAC1, HDAC3, and HDAC8) and enhances the acetylation of histone H4 levels. The curcumin regulates not only gene expression but also can inhibit certain epigenetic enzymes [80]. Other dietary bioactive compounds, flavonoids have potent antioxidant properties, can modulate epigenetic control by the down regulation of pro-inflammatory and inflammatory cytokines and prevent neural impairment in AD [81, 82]. Thus, flavonoids could be a promising therapeutic intervention against neurodegenerative disease. In vivo and in vitro studies showed that the bioactive compound quercetin may regulates cytokines via activation of several downstream molecules such as nuclear factor (Nrf2), Paraoxonase-2, c-Jun N-terminal kinase (c-JNK), Protein kinase C (PKC), Mitogen-activated protein kinase (MAPK) signaling cascades, and PI3K/Akt pathways [83]. Dietary source of component such as cocoa and seed coat of the black soybean, rich source of plant flavonoids and anthocyanin respectively, have been shown neuroprotective action against intellectual deterioration, oxidative stress, neurodegeneration, and memory impairment in a mouse model of AD via the PI3K/Akt/Nrf2/HO-1 pathways [84, 85]. The dietary patterns of coffee and tea that contain bioactive caffeine have been shown to reverse intellectual impairment and reduce the β -amyloid peptides aggregation in the brain in mice model of AD. This

reduction occurs due to the stimulation of protein kinase A activity by the caffeine and increases the phospho-CREB levels, subsequently reducing the phospho-JNK and phosphor-ERK expression in the brain. Thus, the high level of blood caffeine may inhibit the progression to dementia [86, 87]. Dietary pattern of grapes and red wine that contains resveratrol, a polyphenol of potent antioxidant and anti-inflammatory actions [88]. The reactive oxygen species (ROS) induced oxidative stress is protected by the resveratrol by the activation of sirtuin 1 (SIRT1) [89]. Resveratrol also activates a transcriptional coactivator of energy metabolism and several studies have shown that resveratrol supplementation with vitamin D could prevent intellectual impairment in vivo through Amyloidogenic pathways [90, 91]. Another study stated that resveratrol may ameliorate the hippocampal neurodegeneration and memory performance [92]. Insufficient dietary minerals may adversely affect the critical cellular processes associated with intellectual impairment and dementia. Thus, dietary patterns of sufficient minerals may have a protective role against many metabolic diseases including intellectual deterioration [93, 94]. Compelling evidence shows that magnesium deficiency may impair memory and contributes to AD pathology [95]. Magnesium sufficient dietary patterns may modify A β PP processing and stimulate the α -secretase cleavage pathway, thereby protecting the cognitive dysfunction [96].

Dietary patterns of vitamin rich food might be useful in maintaining intellectual function and delaying the progression of AD. Studies have stated that vitamin rich dietary patterns such as folic acid and vitamin B12 can significantly improve intellectual functions [97]. In AD, oxidative stress and mitochondrial dysfunction can be prevented by vitamins, because vitamin can modulate the oxidative stress

Figure 4.
Mechanism of how dietary patterns are involved for the treatment of AD.

markers and misfolded proteins [98, 99]. Clinical studies suggested that ketogenic therapies may be beneficial for AD patients. It was found that plasma ketone levels were increased by the medium chain triglyceride and ketone ester supplementations and improved the intellectual function in AD patients [100]. Another source of fuel for the brain is ketone bodies (KB), which may provide energy for the brain and also increase mitochondrial efficiency and cognitive function. The two forms of KB are very important for these mechanisms in the brain; beta-hydroxybutyrate (b-HB) and acetoacetate. Evidence suggests that brain ketone body utilization is not problematic in AD like glucose, making it an alternative energy source of brain function [101]. **Figure 4** summarized the dietary management of AD.

6. The mechanism of how exercise-eating patterns can modulate the brain function of AD

In the brain of an AD patient, there are several mechanisms for the changes of β -amyloid peptides synthesis and degradation and tau protein modification. Physical activity may change many signaling molecules both at the mRNA and protein level that may induce the anatomical changes of the brain, chemical and electrophysiological change of the nerve, subsequently enhance the plasticity of neurons of the brain and improve the brain function. Multiple paths of physical exercise and dietary pattern are likely enabled to adjust the level of β -amyloid peptides and tau protein directly or indirectly. Both physical activity and habituated dietary healthy food are effective interventions in such a way that can limit the prevalence of neurodegenerative diseases through the minimization of mitochondrial dysfunction in bioenergetics processes [102, 103]. Physical exercise play an important role on neuroplasticity of the brain and cellular energy homeostasis well as improve the cognitive functions by controlling the activation of several signaling molecules such as PGC-1 α and a nicotinamide adenosine dinucleotide (NAD)-dependent deacetylase, SIRT1 [104, 105]. There is a loss of muscle mass and muscle activity with elderly people. Thus, regular exercise and a healthy dietary pattern reduces the development of aging-related muscle deterioration and promotes muscle activity with the older people [106]. Few have shown the that efficacy of exercise with men and women in AD people, even though differences were found in men and women cognitive improvement with exercise. Study showed that exercise can modulate insulin action and as well as blood glucose [107]. In vivo and clinical study have shown the benefit of exercise and dietary pattern as a non-pharmlogical option in reducing the β -amyloid peptides aggregation and tau protein phosphorylation in the aging brain. This mechanism happens less in women rather than men due to the change of hormone level [108]. In vivo study stated that exercise and healthy dietary patterns can reduce cortical BACE1 expression and activity by modulating the MAPK signaling in the cortex in AD patients [109].

Interestingly, animal and human studies have shown that exercise and specific dietary patterns may increase testosterone production but it is depending on the intensity of exercise and exercise-induced testosterone sustained for a long time in the body. It was found that high intensity of exercise can increase testosterone levels in T2DM patients, which is important for the reduction of risk factors of AD [110].

The most important neurotrophins, BDNF (brain-derived neurotrophic factor) is responsible for neurogenesis and synaptogenesis. Not only can the central nervous system (CNS) produce the BDNF but also skeletal muscle through the exercise. The underlying molecular mechanisms of exercise to produce testosterone may be mediated by BDNF production in the brain. Physical exercise may increase testosterone. Thus, exercise and dietary patterns may increase BDNF levels as a stimulus for the

induction of neurogenesis to improve synaptic plasticity [111, 112]. Together physical exercise and dietary patterns not only increase the BDNF but also increase the insulin like growth factor-I (IGF-I). The mechanism of exercise and dietary pattern have been shown to enhance IGF-1 expression in the brain [113]. Moreover, exercise may release several factors like BDNF and IGF-1 into the circulation by testosterone activation. Neurocognitive damage is lifelong incidence with cellular dysfunction. For instance, impairment of BDNF production may influence the synaptic plasticity and neurogenesis in the aging adult brain [114, 115]. Exercise as well as dietary patterns such as low-calorie intake is another important intervention for enlightening metabolic health. The molecular mechanism of low-calorie intake (LCI) is effective against ROS induced-oxidative stress, in which the LCI can reduce β -amyloid peptides aggregation and γ -secretase and plays a preventive role in AD pathology [116, 117]. It was found that the mechanism of low-calorie intake exerts its action by inhibiting nutrient-sensing and inflammatory pathways, thus physical activity and dietary pattern may also be effective methods for the preventive measures of AD [118]. The cellular energy homeostasis is mediated by AMPK in mitochondria, adipose tissue, skeletal muscle, and liver. This mechanism is activated by LKB1 and in response to metabolic stresses, exercise, sex hormones, and insulin sensitizing agents such as Metformin. Thus, the physical exercise and healthy dietary pattern plays a key role in AD patients [119–121]. Oxidative stress and inflammation are the hallmarks of dementia. Individuals' cognitive abilities are related to both non-modifiable factors and modifiable risk factors such as exercise and dietary status. Low calorie diet may be effective against cognitive decline and the high calorie is vice versa [122]. Additionally, some dietary patterns that contain bioactive compounds

Figure 5.
Mechanism of exercise mediated management of AD.

may increase signaling molecules and neuronal hormones that are responsible for cognitive improvement. Diet therapy such as vitamin rich food may affect the bodies' central metabolism as well as brain function, and the production of neurotransmitters for modulation of mood in AD [123, 124]. Conversely, it was found that lack of basic B complex (folic acid, B6, and B12) in the dietary pattern is also proposed to impact on the rate of brain atrophy associated with mild cognitive impairment (MCI) [125]. Strength exercise and other dietary patterns such as intake of seafood and other sources of long-chain omega-3 polyunsaturated fats (LC-n3-FA) may have long-term beneficial effects on cognitive function [126, 127]. Thus, exercise and dietary patterns may balance several factors such as LC-n3-FA act via BDNF, and insulin-like growth factor-1 (IGF-1) can alter the expression of a number of protein pathways in neuronal function, plasticity, and neurogenesis [128]. **Figure 5** summarized the exercise and dietary management of AD.

7. Social inclusion for the treatment of AD

Social inclusion is multidimensional including social and cultural connection with family, friends, work, personal interests and local community, deal with personal crisis etc., and operates at various social levels. In AD, the deterioration of brain activity begins in the hippocampus areas primarily associated with memory and emotion. The deterioration then spreads to other regions, resulting in reduced neuronal processing, eventually associated with episodic memory, emotion and mood, sensation, self-awareness, attention, memory retrieval and theory of mind which is adversely affected in the early stages of AD. Thus, it could be suggested that the brain regions affected by AD may share something in common, including their role of regulating emotion, memory and awareness and social inclusion can significantly affect in a broad range of measures, including a reduction of cognitive decline, reduction in perceived stress, increase in quality of life, as well as increases in functional connectivity, percent volume brain change and cerebral blood flow in areas of the cortex [129–131]. For the treatment of AD, Social inclusion is potentially beneficial in improving the cognitive function of older adults with mild to moderate dementia and improving their quality of life. Thus, it is recognized as a priority field of AD research, as pharmacologic treatments have not demonstrated effective outcomes [132]. Social inclusion may promote communication and enhance social interaction skills that are important for potentially beneficial cognitive functions and domains of memory and recall of older adults with dementia. These non-pharmacological interventions aim to reduce the behavioral symptoms of the AD. For instance, music therapy involves listening to music and singing songs, can modulate the factors involved in cognition and conduct, divert the attention of older adults to provoke emotional responses and modulate them, draw on different cognitive functions, and evoke movement patterns. Another study has indicated that singing traditional songs, which emerged from the life experiences of people living with dementia, activates their implicit memory with a priming effect [133]. Traditional opera can potentially be an effective therapy for improving the cognitive function of older adults with dementia, reducing their behavioral and psychiatric symptoms and enhancing their quality of life [134]. Moreover, it helps improve their memory as well as the coherence and expressiveness of their speech [135]. About ninety percent people with dementia showed behavioral and psychological symptoms and can cause serious complications but reduction of this complication by use of single antipsychotic medications is very difficult. Several studies showed that consideration of both the physical and the social inclusion can promote self-determination and opportunities for meaning and purpose of persons

with dementia [136]. Recent studies concluded that the level of evidence is considered insufficient to support the use of single non pharmacological interventions in prevention efforts of AD; however, mega study reported that around one third of ADs cases worldwide might be attributable to potentially modifiable risk factors such as smoking, physical inactivity, and midlife obesity [137].

8. Conclusion

Single nonpharmacological interventions for the treatment of pathophysiological hallmarks of AD was not sufficient. It should include a new approach of three effector modulations such as exercise–eating pattern and social (EES) activities for the treatment of AD. However, when considering the single modulator exercise, adapting the physical environment is necessary but not sufficient. To effectively address AD, the exercise and eating pattern must also be incorporated into the intervention. Also, when considering social inclusion related to initiatives aimed at decreasing AD, providing initial training is necessary, ongoing training and support to mindfulness, meditation in the form of effective enabling and reinforcing factors must also be included. Finally, development of individualized approaches that promote self-control exercise, eating patterns and social inclusion of persons with dementia. This new approach EES should also be included with other interventions aimed at decreasing AD. Though it is very important that the combination of EES and other interventions would be supportive by the success of interventions. It is our hope that this new approach EES also provides direction for future research and initiatives aimed at successful and sustainable nonpharmacological management of AD.

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