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ORIGINAL ARTICLE **OPEN ACCESS**

Alzheimer 's disease and Factors Involve in the Emergence of AD and Its Treatment Status: A Cross Sectional Survey among General Public

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ABSTRACT

Neurodegenerative disease is an umbrella term used to demonstrate progressive structural and functional neuronal loss and successive neuronal death. Alzheimer's disease is a neurodegenerative disease that is known to affect the person's memory and intellectual abilities. Currently AD is the 6th leading cause of death in US and spite of this only 50% patient are known to be diagnosed. The authors are aimed to assess the prevalence of Alzheimer's disease in men and women, also to reveal to proportionality between age and AD and to enhance the quality of life of these patients by spreading the knowledge among people about the need of symptomatic treatment.A general public survey was conducted among 100 people with the help of a questionnaire which was design in criteria to first diagnose the symptoms of AD in a particular individual, and then find out the genetic factor behind this emergence and other causative factors which may involve in AD including age.Evaluated results were found to be in favor of men as women were AD victims more than two folds of percentage in men and almost all were elderly patients, 30.7% patients belong to age group 65—75 years and 61.5% belong to age group 76—85 years.Women are more prone to AD than men on the account of sexual factor. Age and genetic factors contribute largely in the emergence; AD seems to occur more likely in patients above the age of 60 years. But despite of this there is less awareness among about the requirement of symptomatic treatment to improve their life style.

Keywords: Alzheimer's disease, prevalence, genetic factor, Diet, treatment.

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INTRODUCTION

Alzheimer's disease serves as sixth-leading cause of death in the United State. Only fewer than 50 percent of people with Alzheimer's disease get to the stage of diagnosis [1].AD is a progressive neurodegenerative disease of brain resulting in the gradual diminish of a person's memory and Intellectual abilities, judgmental abilities, interactions, and carry out daily activities of life [2,3]. Alzheimer's disease (AD) comprises a group of dementias that are characterized by presence of amyloid plaques and tangles (neurofibrillary tangles) and dystrophic neurites, as well as the neuronal degeneration and excessive synapses in patients' brains, as histopathological hallmarks. The nano structure revealed by electron microscopy shows, disappearance of microtubules and aggregations of paired helical filaments (PHF), which are predominantly composed of modified form of the microtubule-associated protein tau 1, 2 and 3, that accumulate within dystrophic neurites and neurofibrillary tangles. Hyper phosphorylation of tau is an untimely event in the progression of AD and may precede the disturbance of the microtubule cytoskeleton [7, 8] and also the emergence of PHF-tau [7,9]. Day-to-day scientists are exploring new findings about the causes of Alzheimer's and happenings to the brain with the progression of the disease. Accumulation of beta amyloid (i.e. Protein fragments) is found to form 10-20 years before dementia or even minimal cognitive impairment [4]. According to the analysis of Alzheimer's disease investigators, by the time when the memory begins to destruct and other cognitive problems appear, too much damage to the brain has occurred to be practically reversed by the possible existed treatments [4]. According to a review, in 2010, AD was the basic cause of 83494 deaths and a contributing cause of another 26488 deaths, which makes the illness sixth leading cause of death in United State. Due to increment in Alzheimer mortality, death rates from other diseases—heart disease, cancer and diabetes—decreased

considerably [5]. According to a study based research work it was found that the immunoreactivity of apoE was associated with amyloid in both senile plaques and neurofibrillary tangles. This immunoreactivity was also found in amyloid associated with kuru plaques in Creutzfeldt-Jakob disease [6]. In Alzheimer's disease, tau protein undergoes hyperphophorylation to form tangle which then lead to neuronal degeneration. However, the consequent protein kinases are still mysterious [7].If AD arise before the age 60 then it is more appropriate to call is "The early onset form of AD", which may be due to genetic factor(inherited genetic mutations).Age serves as the greatest risk factor for AD. Late-onset Alzheimer's occurs after 60 years of age and accounts approximately 90—95% of all AD [2]. Women are more prevalent to Alzheimer disease than in men. 0.7% of women and 0.6% of men suffer from the disease in the age group of 65-69 years with increasing incidence of 14.2% and 8.8% in individuals with age 85-89 years.In comparison with men, women have an extended spectrum of dementiarelated behavioral symptoms which predominantly include depression, while aggression is more commonly Sex differences in the AD reported for post-menopausal hormonal changes (lacking of hormone estrogen in females after menopause) [10].

Alzheimer's disease and osteoporosis, occurrence of both diseases found in people aged over 60 years and in clinical practice both diseases are often seen to co-occur [11]. Basically both are multifactorial progressive degenerative disorders. Increasing evidence reveals that osteoporosis and hip fracture are common complexity that are observed in patients with AD, however the mechanisms behind this link isstill remain poorly understood [12]. Researchers have found that there is an association between vitamin D and our brain. Vitamin D receptors exists in many parts of the brain, which means that vitamin D somehow is playing its our brain and may have an impact on the intellectual abilities, thusthe occurrence of Alzheimer's disease may possibly increase in people with low levels of vitamin D (low level of calcium also due to poor calcium absorption) in their body. The evidence collect by epidemiological and basic science suggest a possible correlated pathophysiology between type 2 diabetes mellitus (T2DM) [non-insulin dependent diabetes mellitus (NIDDM) or maturity-onset diabetes mellitus] and Alzheimer's disease (AD). Electroencephalogram (EEG) signals are considered to be functional diagnostic tool to evaluate cognitive disturbances, especially when after the initial clinical procedures any diagnostic doubt still exists [13,14].Atrophy in selected temporal structures indicates towards the diagnosis of Alzheimer's disease, but the absence does not refuse the possibility of early Alzheimer's disease [15]. Neuropathology and structural MRI studies shows that medial temporal lobe (MTL) earliest affected brain region in Alzheimer's disease (AD). Glucose metabolic reductions in the parieto-temporal, frontal and posterior cingulate cortices revealed to be the hallmark of AD through FDG-PET imaging (Fluoro-2-deoxy-D-glucose positron emission tomography. Prediction of future AD and differentiation of AD from other neurodegenerative diseases may be made possible by the cortical metabolic changes [16].Currently only symptomatic treatment for AD is available (i.e. donepezil, rivastigmine, galantamine [ChEI] and memantine) and they do not prevent or reverse the progression of the disease. New disease-modifying interventions are now focusing largely on those compounds that target the amyloid-β pathway. As of now, compounds targeting this pathway, which include tramiprosate and semagacestat, have been seenfailedto show the efficacy in clinical stages of testing. Amyloid-β aggregation is not only responsible for AD but other possible neuronal mechanisms may also involve such as hyper phosphorylated tau, neuronal-inflammation and some other processes play vital roles in the pathophysiology of this multifactorial disorder [17].

The objective of the study is to evaluate the status regarding prevalence of Alzheimer's disease in men and women and also the facts and figures about age factor and complications and to aware the society about the extensive need of treatment regarding AD to provide these patients a better quality of life.

METHODOLOGY

The prevalence of Alzheimer's disease might becoming disastrous to the world with the passage of time and being sixth leading cause of deaths it should be center of attention for the whole field of medical science. In order to help finding the prevalence of Alzheimer disease and its complications and the treatment received by the patients regarding their disease, a survey was conducted. The aim of this survey based study is to check the prevalence of disease as well as how much population might be predispose to AD genetically, by asking them about their family history of AD and also to spread knowledge about the treatment options and the need of treatment among the people. For this purpose a questionnaire was designed that accommodate all the necessary questions to judge the existence of AD and the family history about AD to rate the genetic factor. Also possess queries about the dietary habits which may contribute to AD and about the treatment they are receiving and most importantly to judge that they either taking treatment for this irreversible degenerative disease or not. Basically to avail their family members to know about the treatment necessity and thus helping that suffering individual, who is

bore to death, is one of the objective for this cross sectional study.This survey was conducted in general public, in different age groups from 18 years till 85 years to catch on the relation between the age and Alzheimer's disease. The total sample size was 100 given in table 1.

Table 1 sample size distribution

MALE POPULATION	***AGE GROUP (years)***	***NO. OF PARTICIPANTS***	***TOTAL NO. OF MALE PARTICIPANTS***
	18—29	20	50
	30—59	10	
	60—85	20	
FEMALE POPULATION	***AGE GROUP***	***NO. OF PARTICIPANTS***	***TOTAL NO. OF FEMALE PARTICIPANTS***
	18—29	20	50
	30—59	10	
	60—85	20	

RESULTS

After extensive study over the AD multiple facts and figures arise to be the center of attention. According to **Figure 1** Females are more prone to Alzheimer's disease on account of sexual factor whose actual cause is still not familiar evidently. Thus the percentage of AD in females is more than twofold of the percentage in men.

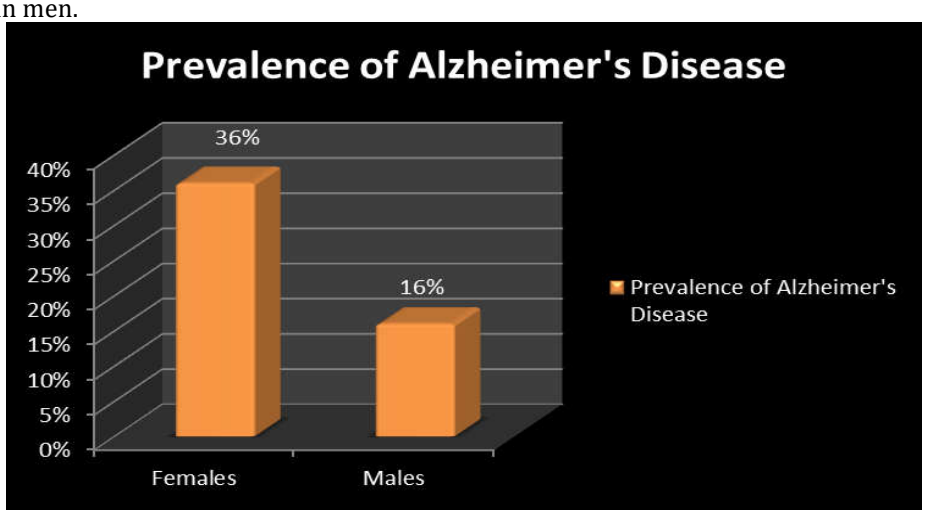

Figure 1.Prevalence of AD in males and females

This study also showed that many diseases may correlate with AD or may be a basic cause of AD. Mostly patients diagnosed with AD were having different heart diseases. High cholesterol intake could be a major reason for AD and hypercholesterolemia may be an indication for being suffer from AD.

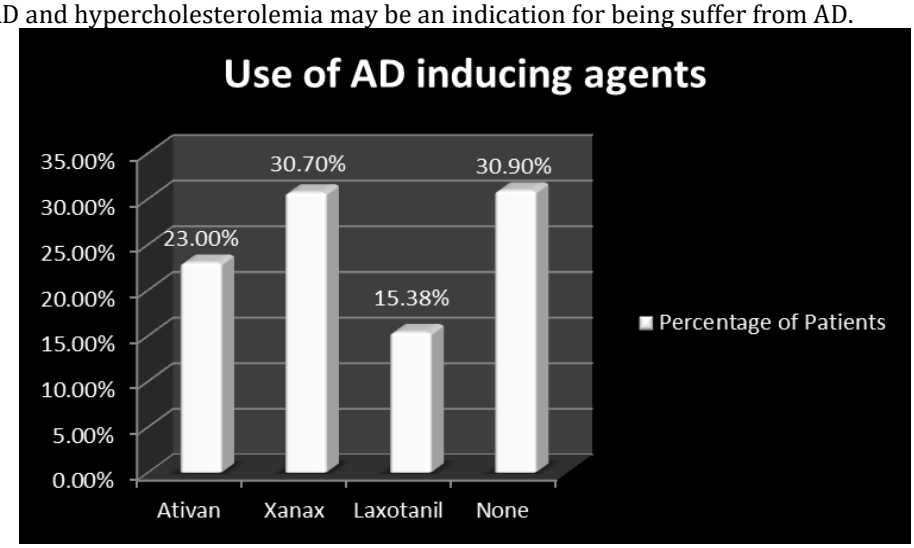

Figure 2.Agents that induce AD

Information in figure 2 gave us an idea that benzodiazepines being sedatives/hypnotic may involve in the induction of AD and may play a key role in progress of Alzheimer's disease. These patients were taking different benzodiazepines since past few years which may be an integral part of their AD progression.
AD is also a genetically transmitted disease and which is clearly proven by the data collected, which shows that most of the AD patients were predisposed to AD genetically 61.50% and may be as a result of this matter of fact, they are now suffering from AD.

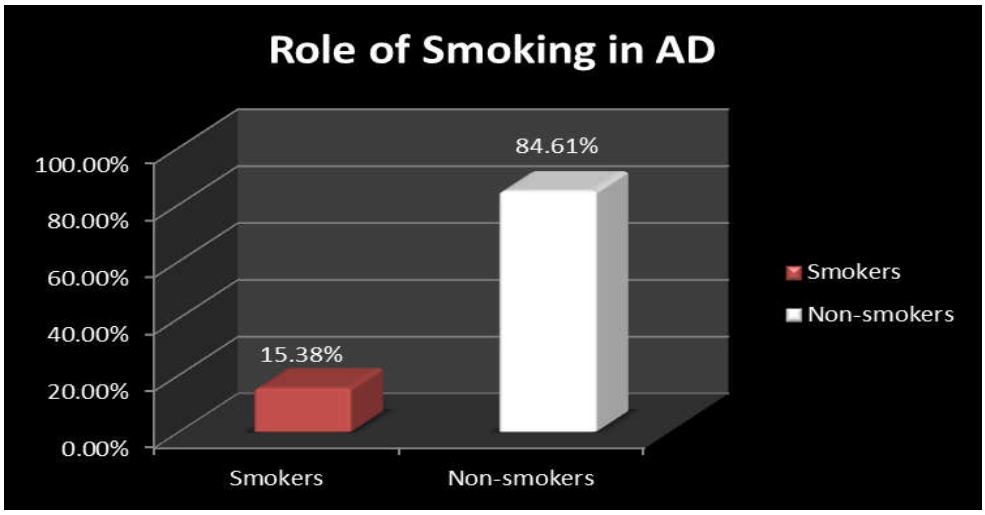

Figure 3.Role of smoking in AD

According to the facts as shown in figure3 smoking may be somehow responsible to cause AD. These smoker patients were used to smoke on daily basis and they were addicted to smoking.
These Alzheimer's patients were mostly anti-socialistsmale 50% and female 55.50% respectively.They mostly want to stay at home alone or only with their close blood relatives. They don't want to go out and meet people and prohibited to attend social events and chats. This study revealed the part of anti-socialism behind the AD; females are more likely to be anti-socialists than males.

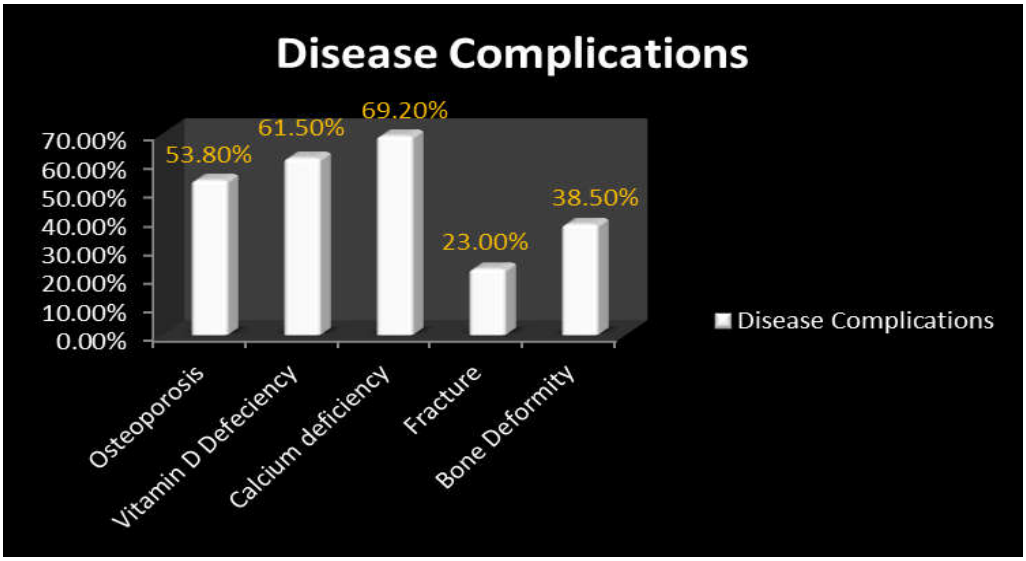

Figure 4.Disease Complications

Osteoporosis, vitamin D and calcium deficiency, bone deformity, they all are disease complications associated with AD as indicated in figure 4. Every disease appears with its related complications which can be use as primary diagnostic tools of that disease. Family of these Alzheimer's patient's complaint about their weak bones and fracture complications which could be an outcome of AD.
Only fewer patients were receiving their treatment which was 38.46% regarding Alzheimer's disease. There may be many facts behind this lower treatment percentage. Patients of AD moderate to severe are

not in their senses to pay attention about their treatment. These patients are completely relay on their family.

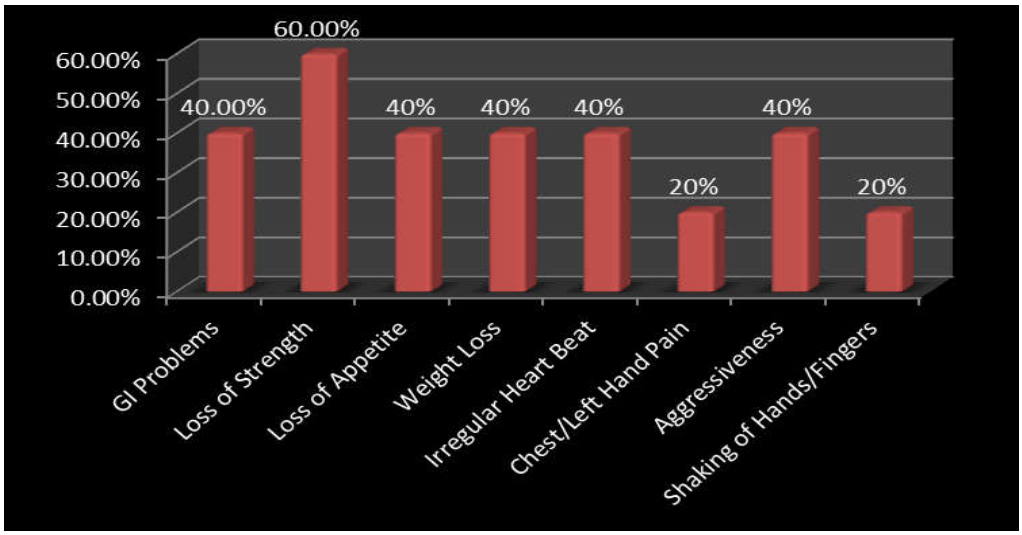

Figure 5.Adverse effects regarding treatment

Every treatment exhibits its adverse reactions along with useful effects. According to details that are quoted in figure 5, the treatment of AD also manifests its side effects in form of GI problems, irregular heartbeat, shaking of hands and so on in patients taking treatment regarding AD. Many of the family members of these Alzheimer's patients were taken this disease for granted and they thought that AD is just a manifestation of being old. Some patients were taking alone therapy or core therapy with Exelon (rivastigmine) 40% and some were taking combination therapy as a result of moderate to severe AD. Exelon (rivastigmine), Aricept (donepezil), Cognex (tacrine), they all are ChEI while Namenda (memantine) is N-methyl-D-aspartate (NMDA)-receptor antagonist or we can say Antiglutamatergic agent.

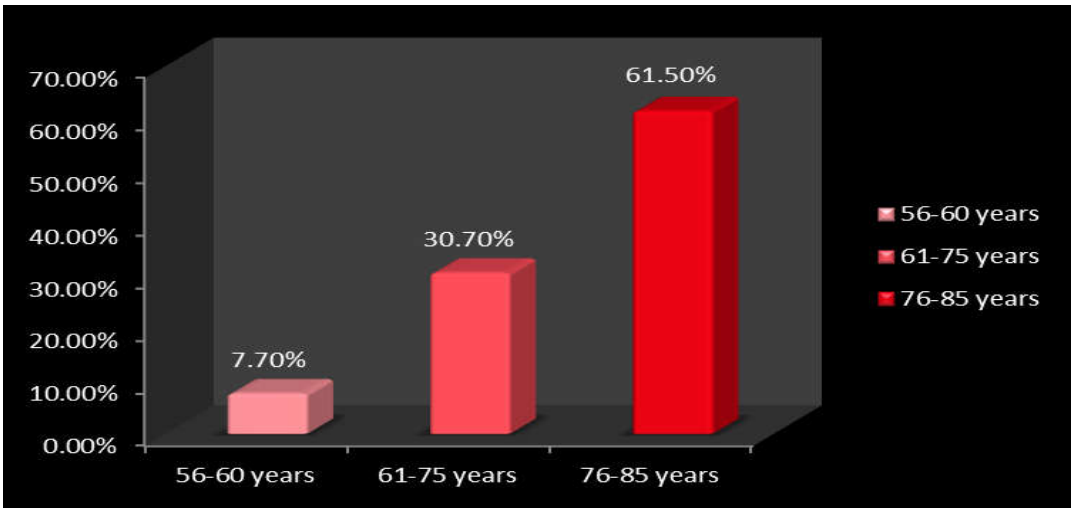

Figure 6.Age group prone to AD (relation between AD and age)

AD is an age related progressive disease which means that AD has a direct relation to age, which is clearly shown in figure 10. The older the patient, the greater will be the possibility of AD, that means older people are more prone to AD as shown in figure 6.

DISCUSSION

In AD all the intellectual abilities of a person diminish as a result of neurodegeneration and the patient felt difficulty in carrying out routine work. Complications of AD are so vast which makes it an important issue to look upon the treatment status consciously. AD is more prevalent to women than men whose reason still remains poorly understood. Genetic factor is also an underlying causative factor which plays a key role in the emergence of AD. In AD there are amyloid plaques and tangles with progressive degeneration of neurons and excessive synapses in patients' brains which serves as a diagnostic hallmark.

Microtubules disappear and paired helical filaments (PHF) show aggregations, composed of modified form of the tau protein 1, 2 and 3 and forms tangles which can be visibly shown in Nano structure by electron microscopy. Scientists are continuously in search of causative factors of AD and what changes occur to brain by the progression of the disease. 10—20 years before the emergence of dementia, beta amyloid formed in the brain with slight cognitive impairment. According to an investigation, the time when cognitive and memory problems start to appear is the time when too much damage has been occur to the brain. Tangles are formed in AD by hyper phosphorylation of tau protein in AD which leads to neuronal degeneration. Early AD (i.e. before 60 years) may involve inherited gene mutation. Late onset of disease (i.e. after 60 years) constitutes about 90—95% of all AD. Women are more susceptible to AD than men due to sexuality factor. In AD, women potentially possess behavioral symptoms like depression whereas aggressiveness seems to appear in men. Post-menopausal hormonal changes may contribute in sexual factor for AD (lacking of estrogen).Acetylcholine (ACh), noradrenaline, serotonin, somatostatin, and corticotrophin-releasing factors are cerebral neurotransmitters and AD is associated with reduced levels these neurotransmitters, whereas the glutamate levels increase[18,19]. Thus, AD treatment requires the restoration of Ach neurotransmitters which may possible by several ways such as exploitation of ACh precursors (eg, lecithin or choline), using muscarinic or nicotinic agonists (eg, bethanacol, arecoline, and milameline), as well as by administrating cholinesterase inhibitors (ChEIs)[18,20,21]. ChEIs, being first class of anti-AD drugs approved by the United States FDA, which by inhibiting cholinesterase (acetylcholinesterase [AChE] and/or butyrylcholinesterase [BuChE]) reduce the hydrolysis of acetylcholine in the synaptic cleft. ACH levels increase as a result of this inhibition and therefore improves neurotransmission [18,23]. There is also Antiglutamatergic treatment present in shape of memantine (nemenda) that reduced clinical deterioration in moderate-to-severe Alzheimer's disease [24]. Alzheimer's disease and osteoporosis are co-related diseases and often seen to co-occur. There are receptors of vitamin D in our brain which may have their role in memory and other intellectual abilities and due to this fact there are chances of AD in patients with low levels of vitamin D. As calcium is an important component of cell signaling, the deregulation of calcium-mediated signaling occurs in Alzheimer's disease. Cardiac disease and high cholesterol diet contributes in the accumulation of Alzheimer's disease-like β-amyloid within brain neurons. Toxicities of some drugs also contribute to the emergence of AD like benzodiazepines. Long term and persistent use contributes to increase the risk of Alzheimer's disease. Malnutrition and weight loss can also be involved in AD progression. Thus, treatment of weight loss and malnutrition may also be an important part of AD treatment criteria.Diet rich in polyunsaturated fatty acids might seems to be good for AD patients while on the other side, transfatty acid might potentially increase risk of AD and may contribute to an earlier onset of the disease. If there is shortage of insulin in the body, glucose exposure will be great and there are multiple proteins in neurons that are susceptible to glycation which increases the risk of AD as in case of type II diabetes mellitus. Therefore, a high carbohydrate diet may be harmful to AD. Similarly, heavy alcoholism (greater than 2 drinks), together with heavy smoking and APOE epsilon4 carriers, may also associate with an earlier onset of AD.As Calcium involve in normal functioning of the cells considerably. Deregulation of calcium-mediated signaling seems to occur in many neurodegenerative diseases including AD. Calcium homeostasis alter by expression of familial Alzheimer's disease (FAD) mutants of presenilin (PS) and amyloid precursor protein (APP) that have been shown by studies in neurons and mice expressing Alzheimer's disease-associated transgenes and then cause synaptic dysfunction and dendritic spine loss in neurons . Alzheimer's disease-like β-amyloid deposits within brain neurons non-demented individuals with cardiac disease and high cholesterol diet. Heart disease may serve as prevalent finding in Alzheimer's disease, and may be a predecessor to the dementing disorder. According to a review in 2000, the whole team found production and accumulation of β-amyloid in the brain in a cholesterol-fed rabbit model of human coronary heart disease. This accumulation of β-amyloid can be reversed or swapped by removing cholesterol from the rabbits' diet, which clearly indicates the association between heart disease, cholesterol and Alzheimer's disease.

It has been assumed that AD is might be 'type 3 diabetes'. Some clinical trials were searched for the applicable information in concern with the testing of antidiabetic drugs in AD patients. There are evidences present for connection between T2DM and AD based on a number of multiple studies, but the actual definite biochemical mechanisms remain poorly known. Blood flow to the brain impaired by sustained elevation of blood glucose and then may contribute to progressive neurodegenerative disorder like Alzheimer. Benzodiazepines are most likely to prescribe to elderly patients for many psychological conditions. But there are evidences for benzodiazepines toxicities too, which may also include incidence of Alzheimer's disease in elderly patients. Short term use does not risk Alzheimer's disease but long term and persistent use contributes to increase the risk of Alzheimer's disease [16].Malnutrition and weight loss are common are frequent complexities of AD, and the mean prevalence of malnutrition in domestic

AD patients as reported by Guigoz *et al* is about 5% and a minimum lower nutritional status was reported to reveal the progression of AD . Weight loss was reported to estimate the rapid cognitive detoriation in AD patients, thus treatment of weight loss and malnutrition may also be an important part of AD treatment criteria. Current evidence suggests that elevated intake of polyunsaturated fatty acids rich diet might seem to be beneficial to AD .While on the other side, transfatty acid might potentially increase risk of AD and may contribute to an earlier onset of the disease by increase of amyloidogenic and decrease of nonamyloidogenic processing of amyloid precursor protein which successively increase the Aβ production. If we took a glance towards the carbohydrate intake, then it should be noticeably important that type two diabetes mellitus patients are more susceptible to AD as they lack insulin thus increased glucose exposure and there are multiple proteins in neurons that are susceptible to glycation, which may serves as an important contributor to AD . Therefore, a high carbohydrate diet may be harmful to AD .Epidemiological studies suggest that light-to-moderate alcohol consumption may associated with a reduced risk of AD, especially among APOE epslion4 non-carriers]. Whereas, heavy drinking (greater than 2 drinks), together with heavy smoking and APOE epsilon4 carriers, May related with an earlier onset of AD. Besides this, there are many foods too which reduce the risk of Alzheimer. Epidemiological studies suggest that fish consumption can reduce markedly the risk of demented disorders and AD, especially among people who are APOE epslion4 non-carriers. According to a cross sectional study conducted from 1993-2000, it was found that participants who consumed fish at least once per week or more had 60% less risk of Alzheimer disease compared with those who hardly ate fish .Similarly, frequent consumption of fruits and vegetables might also decrease the risk of AD and dementia. Along with factors that induce AD there are many factors/foods too that reduce the risk of AD. Fish consumption is reported to reduce the risk of demented disorders and AD, especially in APOE epslion4 non-carriers. Similarly, fruits and vegetables might also decrease the risk of AD.EEG signals can be a better diagnostic tool to evaluate cognitive disturbances. Atrophy of brain especially temporal structures indicates towards the AD. Medial temporal lobe (MTL) is known to be the earliest affected brain region in Alzheimer's disease. FDG-PET imaging shows Glucose metabolic reductions in the parieto-temporal, frontal and posterior cingulate cortices in AD and these cortical metabolic changes can be use in future prediction of AD. Presently, only symptomatic treatment is available which only controls the symptoms not to stop or reverse the progression. Treatment include AChI and also Antiglutamatergic treatment which include only one agent i.e. memantine.

By collecting the whole data by the public survey questionnaire we came to know that yes it is indeed a fact that women are more prevalent to Alzheimer's disease than men whose reason is not clearly known but some professionals suggest that it may be a function of decreased estrogen level in females after menopausal phenomenon. Practically there may be other diseases responsible for the occurrence of AD in these patients and we found that heart disease may likely to contribute largely to cause AD as 69.2% patients with AD were having complained of their heart disease and the reason behind this correlation may be due irregular/reduced blood flow towards brain and thus damage to brain tissue and neurons. Diabetes mellitus may also play a key role in AD progression due to increased exposure of glucose and decreased insulin level. Similarly high cholesterol diet increases the risk of AD. According to the collected statistical data of Alzheimer's patients, most of the patients use to take different benzodiazepines, which reveal a fact that they may have an impact on the progression of AD and may serves as AD inducer agents. Even the use of benzodiazepine might also serve as use an early marker of conditions associated with an elevated risk of dementia. Thus long term use of these sedative/hypnotic drugs should be considered as a public health concern. Genetic factor contributes a lot which has been proved experimentally by this study. About 61.5% of the Alzheimer's patients were genetically predisposed to the AD. They may inherit with the mutant gene responsible for AD. Some drastic habits like Alcohol use and smoking may also be a part of AD risks. This study found that 15.38% of the patients were smoker which may be a minimal supportive factor in the progression of AD as smoking is known to increase the risk of cancer and heart disease it may also increase the risk of AD as they all are interlinked.To be an antisocialist may also be a fundamental cause of AD and females are more likely to be antisocialists; they want to stay at home and so their thoughts become confined and the need of brain cells become limited so degeneration of neurons start as a result. Many disease complications occur as a manifestation of AD, like osteoporosis, vitamin D and calcium deficiency, bone deformity; there is comorbidity between these conditions and AD. There are vitamin D receptors present in pour brain and where they perform their vital functions, when there is vitamin D deficiency there will be calcium deficiency, and when there is calcium deficiency then calcium mediated cellular channels also become effected and which will in turn responsible for abnormal synapsis and thus neuronal degeneration. And this calcium and vitamin D deficiency will contribute to osteoporosis and other related bone disorders.

Despite of these disastrous outcomes of AD, many few of patients are taking treatment regarding AD which may be a sign for lacking of awareness among people or misconceptions about the treatment. Only 38.46% patients were taking the regarding treatment. Another reason for lower treatment percentage may be a misconception among the people about the disease, most of the people thought that this is not a disease but only a manifestation of being old.Exelon, Aricept, Cognex, Namenda are some treatment options in which first three are AChI and the Namenda is a NMDA blocker. Among patients who are receiving the treatment, mostly (about 40%) patients were taking Exelon alone as a core therapy, but no patient were using the other agents as an alone therapy, they all use other agents then Exelon in combination therapies; i.e. 40% patients were taking Namenda along with Aricept and 20% patients were receiving a combination therapy of Cognex, Aricept and Namenda for better results for their moderate to severe AD. These patients also complaint about the adverse effects regarding their treatment which includes, weakness/loss of strength, GI problems, loss of appetite, weight loss, irregular heartbeat, chest/left hand pain, aggressiveness and shaking of hands/fingers. Despite of this, treatment of AD is so necessary to take because there is a benefit-to-harm ratio of every treatment and if the treatment shows benefits than harm, then the treatment is considered to be safe and can be continue without any doubt. AD is an age related disease and is most popularly known to affect the elderly patients. According to statistical data of this survey, it is found that only 7.7% patients were 56—60 years old and all others were above 60 years of age. 61—75 year age group accounts 30.7% of all the Alzheimer's patients while 76—85 year age group constitutes 61.5% of all Alzheimer's patients. This relation shows that with the increase in age, risk of AD also increases; thus it is revealed that there is a direct relation between the age and AD.

CONCLUSION

Sex, genes and age are the main causative factors of AD. Due to this reason females, genetically predisposed and elderly patients are more prone to AD. The death rate due to Alzheimer's disease is increasing day by day which is an indication that all medical professionals should pay attention towards this disease to provide the victims a better quality of life through early diagnosis and by promoting the regarding treatment. It is also important to spread this knowledge among people that it is not only an age manifestation but a diseased condition which can be slow down by treatment.

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