THE RELEVANCE BODY MASS INDEX ON THE OXIDATIVE STRESS STATUS OF ALZHEIMER'S DISEASE PATHOLOGY

ELENA-LOREDANA SANDU[1*], CIOBICA ALIN[1], LACRAMIOARA OPRICA[1], EMIL ANTON[2], DANIEL TIMOFTE[2]

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Abstract

Introduction: While dementia affects 6-10% of persons 65 years or older, industrialized countries have witnessed an alarming rise in obesity. Obesity affects over 500 million people worldwide, and has far reached negative health effects. In addition, oxidative stress is a risk factor for metabolic diseases and was previously shown to be independently associated with obesity.

Current status of research: Researchers investigated the relationship between body mass index (BMI), age and oxidative stress. In this way, convincing evidences demonstrated that oxidative stress is a prominent feature in Alzheimer disease and links oxidative stress to the development of neuronal death and neural dysfunction, which suggests a key pathogenic role for oxidative stress in AD. Moreover, the disease progression is enhanced by oxidative stress. Also, while many hypotheses have been provided as the causes of the disease, the exact mechanisms remain elusive and difficult to verify. Results demonstrate that oxidative stress increases with the increasing of BMI and age, as a sequel to an impaired antioxidant status, an increase of peroxides and uric acid and a disadvantaged lipid profile.

Conclusions: Future studies are needed to understand optimal weight and biological mechanisms. Oxidative stress and inflammation are implicated in the pathogenesis of obesity and its related complications.

INTRODUCTION

Obesity affects over 500 million people worldwide, and has far reaching negative health effects. Oxidative stress is a risk factor for chronic diseases and was previously shown to be independently associated with obesity.

Obesity is a chronic disease of multifactorial origin that develops from the interaction of social, behavioral, psychological, metabolic, cellular, and molecular factors (Kaufer et al., 2001). It is the condition under which adipose tissue is increased and can be defined as an increase in body weight that results in excessive fat accumulation. The World Health Organization (WHO) defines obesity as a body mass index (BMI) > 30 and defines overweight as with a BMI of 25 (Sikaris et al., 2004).

Adiposity, commonly measured as body mass index (BMI), may influence or be influenced by brain structures and functions involved in dementia processes. Adipose tissue changes in degree and intensity over the lifespan, and has been shown to influence brain development in relationship to early and late measures of cognitive function, intelligence, and disorders of cognition such as dementia. A lower BMI is associated with prevalent dementia, potentially due to underlying brain pathologies and correspondingly greater rates of BMI or weight decline observed during the years immediately preceding clinical dementia onset. However, high BMI during mid-life or at least approximately 5-10 years preceding clinical dementia onset may increase risk. The interplay of adiposity and the brain occurring over the course of the lifespan will be discussed in relationship to developmental origins, mid-life sequelae, disruptions in brain structure and function, and late-life changes in cognition and dementia. Characterizing the life course of adiposity among those who do and do not become demented enhances understanding of biological underpinnings relevant for understanding the etiologies of both dementia and obesity and their co-existence.

Researchers investigated the relationship between body mass index (BMI), age and oxidative stress. In this way, convincing evidences demonstrated that oxidative stress is a prominent feature in Alzheimer disease and links oxidative stress to the development of neuronal death and neural dysfunction, which suggests a key pathogenic role for oxidative stress in AD. There is increasing evidence for the role of total adiposity, usually measured clinically as body mass index (BMI), and central adiposity, measured in AD. This topic is of enormous public health importance given the global epidemic of high adiposity and its consequences.

Alzheimer's disease (AD), the most common form of dementia among the elderly, is characterized by the progressive decline of cognitive function and has a detrimental impact globally. The number of AD cases worldwide was estimated at 36 million in 2010 and is predicted to triple by 2050.

Oxidative stress is a major factor in the aging process and in the course of various diseases associated with aging, such as AD. Oxidative stress, the direct result of the imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and intracellular antioxidant defenses, is invariably involved in the onset of diabetes and neurological pathologies such as Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis. Diabetes, in many cases, usually results in further complications such as cardiovascular disease, atherosclerosis,

and diabetic nephropathy. Thus, the hypothesis of diabetes leading, in part, to the onset of AD is an appealing topic and is hotly debated in the current literature.

OBJECTIVE

This review comprehensively examines the current knowledge on the relationship between body mass index (BMI), oxidative stress and dementia. Understanding the life-course changes in BMI and their influence on dementia risk, cognitive prognosis and mortality after diagnosis may provide new insights into the underlying pathophysiology of dementia and shape possible intervention and treatment strategies. These observations provide a strong base for addressing biological mechanisms underlying this complex association.

CURRENT STATUS OF RESEARCH ON THE OXIDATIVE STRESS OF ALZHEIMER'S DISEASE

With the emergence of disease-modifying strategies for the treatment of AD, impetus to diagnose the condition in its early 'preclinical' stages – before significant brain damage occurs – has intensified. Fortunately, advances in technology and in our perspective on what defines AD may soon make such antecedent diagnosis possible.

Dementia is an acquired syndrome in which there is a decline in memory and thinking that is sufficient to interfere with everyday performance. Some individuals demonstrate deficits either in memory alone or in memory and other cognitive domains that are indicative of an abnormality but are not yet severe enough to be termed "dementia". Most people who go on to develop dementia go through a transitional stage that some term very mild dementia and others term mild cognitive impairment (MCI) or 'cognitively impaired no dementia' (CIND). There are many different entities which can lead to cognitive impairment and dementia, including a variety of neurodegenerative disorders, vascular damage, infections, tumors, and other causes. AD is the most common cause of cognitive impairment and dementia in people over the age of 65. Determination that acquired cognitive impairment or dementia is present, and diagnosis of its likely cause, is based on clinical history (especially from a reliable informant), neurological and psychiatric examinations, and certain laboratory tests.

Recent advances indicate that dementia risk is modified by perinatal events, education status, nutritional intake, degree of physical activity and cognitive and social engagement (Borenstein et al., 2006). Several of these factors impact on adult-onset vascular disorders including strokes, hypertension, atherosclerotic disease, atrial fibrillation, diabetes mellitus, dyslipidemia, hyperinsulinaemia, hyperglycaemia, hyperhomocysteinemia, and obesity (Luchsinger et al., 2005). It is increasingly recognized that factors which increase cardiovascular disease or brain vascular pathology exacerbate the onset or progression of late-onset dementias. While data vary in individual studies that may relate to the clinical diagnosis of dementia, carriers of the apolioprotein E ε4 allele in general appear at greater at risk in the presence of vascular disease. However, the evidence for single clinically defined cardiovascular risk factors being associated with incident AD is inconsistent (Purnel et al., 2009). Some genetic influences or environmental factors may modify the progressive changes which define the final phenotype and burden of brain pathology (Premkumar et al., 1996). While randomized or controlled trials of risk factor modification (with multiple simultaneous interventions) are lacking it is encouraging that interventions of cognitive and physical activity were shown to improve cognitive performance and slow cognitive decline (Middleton et al., 2009).

As with other age-related diseases (cardiovascular disease, diabetes, cancers, etc), there are likely to be behavioral, dietary and other environmental factors that may affect the risk of AD. However, this area of research has not yet matured to a point where clear recommendations can be made. Epidemiological findings suggest that a low education level, history of head trauma, consumption of high calorie – high fat diets and a sedentary lifestyle may each increase the risk of AD (Mattson, 2004).

Changes in lifestyle and diet have resulted in an increase in the number of obese subjects; obesity has been regarded as an important factor in causing various health problems. The central nervous system (CNS), by means of signals, regulates appetite, energy intake, and weight gain; obesity can result from a failure of these signaling pathways (Sikaris, 2004).

Obesity is considered the largest public health problem worldwide, especially in industrialized countries (Bravo et al., 2006). Obesity increases mortality and the prevalence of cardiovascular diseases, diabetes, and colon cancer (Amiekhizi et al., 2007). Substantial literature has emerged that shows that overweight and obesity are major causes of co-morbidities, including T2DM, cardiovascular diseases, various cancers, and other health problems, which can lead to further morbidity and mortality. The related health-care costs are also substantial. Therefore, a public health approach to

develop population-based strategies for the prevention of excess weight gain is of great importance. However, public health intervention programs have had limited success in tackling the rising prevalence of obesity.

Alzheimer's disease (AD) is a complex, multifactorial, heterogeneous mental illness, which is characterized by an age-dependent loss of memory and an impairment of multiple cognitive functions. AD is associated with the presence of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid beta (Aβ) plaques, the loss of neuronal subpopulations, mitochondrial oxidative damage, synaptic loss, and the proliferation of reactive astrocytes and microglia (Selkoe, 2001). With the life span of humans increasing and with decreasing cognitive function in elderly individuals with AD-related dementia, AD has become a major health problem in society. Therapeutic interventions are urgently needed to minimize the ill effects of this devastating disease. Genetic mutations are responsible for causing early onset “familial” AD (constituting only 2% of AD cases), but the causal factor(s) for the vast majority of late-onset “sporadic” AD cases is still unknown.

Histological, pathological, molecular, cellular, and gene expression studies of AD have revealed that multiple cellular pathways are involved in AD progression (Mattson, 2004). Pathologically, there are no differences between early- and lateonset AD (Anekonda et al., 2005). Several factors are known to be involved in the development of late-onset AD, with two of the major ones being aging (Selkoe, 2001) and mitochondrial abnormalities (Reddy, 2006; Zhu et al., 2005; Sullivan et al., 2005). Other contributing factors are the ApoE genotype (Raber et al., 2004), insulin-dependent diabetes (de la Monte et al., 2005), and environmental conditions, including diet (Kitozawa et al., 2004).

Recent cellular and animal model studies revealed that AD progression involves such cellular changes as inflammatory responses, mitochondrial oxidative damage, synaptic failure, and hyperphosphorylation of tau, all of which are directly related to aging and Aβ production (Kitozawa et al., 2004; Reddy et al., 2004, 2005; Manczak et al., 2004).

Oxidative stress is a major factor associated with the development and progression of AD and other forms of dementia. A large body of data suggests that free radical oxidative damage—particularly of neuronal lipids (Markesbery et al., 1999), nucleic acids (Manczak et al., 2004; Pappolla et al., 1996, 1999), and proteins (Pappolla et al., 1996, 1999; Butterfield et al., 2001) is extensive in the brains of AD patients. Increased oxidative stress is thought to result in the generation of free radicals and ROS, which is reported to be released by microglia activated by Aβ (Qin et al., 2002). Compared to other organs, the brain has been found to be more vulnerable to oxidative stress due to its high lipid content, its relatively high oxygen metabolism, and its low level of antioxidant defenses (Butterfield et al., 2001;). Markers of oxidative stress, such as 8-hydroxyguanosine and hemeoxygenase, have been localized to pathologic lesions in the brains of AD patients (Smith et al., 1994).

The free radical theory of normal aging proposes that the slow generation of oxygen free radicals, an unavoidable consequence of life in an aerobic environment, results in cumulative damage to critical cellular components, and eventually leads to age-related pathology (Harman et al., 1994). Free radical-mediated damage to neuronal membrane components have been implicated in the etiology of many neurodegenerative disorders, especially Alzheimer disease (Butterfield et al., 1994; Hensley et al., 1996), in which one of the most dominant risk factors is age.

According to the free radical theory of aging, reactive oxygen species cause oxidative damage, proposed to be an underlying factor of the aging process. There is considerable literature to suggest that free radical scavengers can be used to prevent free radical damage in a variety of systems.

Oxidative stress occurs due to an imbalance in the levels of antioxidant defense systems and production of reactive oxygen/reactive nitrogen species. Oxidative stress has reported to be important in the pathophysiology of a number of age-related diseases, including Alzheimer disease (AD). AD is characterized by the presence of three principal pathological hallmarks: synapse loss, extracellular senile plaques (SP), and intracellular neurofibrillary tangles (NFTs). The major component of SP is amyloid β-peptide (Aβ), a 40–42 amino acid peptide that is derived from proteolytic cleavage of an integral membrane protein (Duyckaerts et al., 2009).

ROS occur under physiological conditions and in many diseases and cause direct or indirect damage in different organs; thus, it is known that oxidative stress (OS) is involved in pathological processes such as obesity, diabetes, cardiovascular disease, and atherogenic processes. It has been reported that obesity may induce systemic OS and, in turn, OS is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome (Esposito et al., 2006). The sensitivity of CRP and other biomarkers of oxidative damage are higher in individuals with obesity and correlate directly with BMI and the percentage of body fat, LDL oxidation, and TG levels (Pihl et al., 2006); in contrast, antioxidant defense markers are lower according to the amount of body fat and central obesity (Chrysohoou et al., 2007; Hartwich et al., 2007). A research showed that a diet high in fat and carbohydrates induces a significant increase in OS stress and inflammation in persons with obesity (Patel et al., 2007).

Several epidemiological show that a history of adult onset diabetes mellitus increases the risk of cognitive impairment and dementia in the elderly (Ott et al., 1996). Risk for AD and particularly VaD was reported to be 2–2.5 fold greater among type II diabetics, irrespective of age at which diabetes occurs. Several scenarios including impaired insulin signalling induced neurodegenerative changes, advanced glycation of neuronal components, oxidative stress and inflammatory mechanisms have been proposed.

Features of the insulin resistance syndrome have also been associated with low cognitive function (Kalmijin et al., 2000) and with AD (Kuusisto et al., 1997). The risk is even higher in individuals expressing components of the metabolic syndrome including high blood pressure, increased triglycerides, high blood glucose, low LDL cholesterol and obesity (Whitmer et al., 2007). Moreover, obesity and overweight in midlife, measured by body mass index and skin-fold thickness, are strongly associated with an increased risk of both AD and VaD, independent of the development of diabetes or other cardiovascular-related morbidities. Conversely, higher baseline body mass index and slower declining body mass in late life appear to reduce risk of dementia (Hughes et al., 2000). This suggests that a faster decline in body mass index in late life is a preclinical indicator of an underlying dementing illness, especially for those who were initially overweight (Hughes et al., 2000).

The increase in obesity-associated OS is probably due to the presence of excessive adipose tissue itself, because adipocytes and preadipocytes have been identified as a source of proinflammatory cytokines, including TNF-α, IL-1, and IL-6; thus, obesity is considered a state of chronic inflammation. These cytokines are potent stimulators for the production of reactive oxygen and nitrogen by macrophages and monocytes; therefore, a rise in the concentration of cytokines could be responsible for increased OS. Obesity increases the mechanical load and myocardial metabolism; therefore, oxygen consumption is increased. One negative consequence of increased oxygen consumption is the production of ROS as superoxide, hydroxyl radical, and hydrogen peroxide derived from the increase in mitochondrial respiration and, of course, from the loss of electrons produced in the electron transport chain, resulting in the formation of superoxide radical (Khan et al., 2006).

Mitochondria provide the energy required for nearly all cellular processes that ultimately permit the carrying out of physiological functions; additionally, they play a central role in cell death by the mechanism of apoptosis. Mitochondrial dysfunction has been implicated in a variety of diseases ranging from neurodegenerative diseases to diabetes and aging. Obesity takes place in disorders that affect mitochondrial metabolism, which favors ROS generation and the development of OS. On the other hand, another mechanism has been proposed that involves an effect of high triglyceride (TG) on the functioning of the mitochondrial respiratory chain, in which intracellular TG, which is also high, inhibits translocation of adenine nucleotides and promotes the generation of superoxide (Monteiro et al., 2010).

The mitochondrial process of oxidative phosphorylation is very efficient, but a small percentage of electrons may prematurely reduce oxygen, forming potentially toxic free radicals, impairing mitochondrial function. Beyond that, under certain conditions, protons can be reintroduced into the mitochondrial matrix through different uncoupling proteins, affecting the control of free radical production in mitochondria (Martinez et al., 2006).

In AD, oxidative stress can alter the functions of TCA enzymes as well as induce intracellular accumulation of calcium, which may lead to cellular death (Fu et al., 1998;). Dysfunction of TCA enzymes may compromise cellular energetics and elevate oxidative stress further (Smith et al., 2000). If not intervened, this feed-forward loop may accelerate the progression of the disease. Various studies have proposed using antioxidant therapeutics to prolong the time of onset of AD or retard the rate of its progression (Opii et al., 2008; Behl et al., 2002;). In the same study, co-treatment of cells with N-acetyl cysteine showed much better protection from oxidative stress than lipoic acid or N-acetyl cysteine alone (Moreira et al., 2007). Apart from acting as an antioxidant itself, lipoic acid in the reduced form can also reinforce other water-or lipid-soluble antioxidants such as glutathione, ascorbate, and vitamin E by scavenging their radicals (Kagan et al., 1992).

Using PC 12 cells and Aβ (25–35) peptide, Bozner et al. studied the connection between Aβ and mitochondrial DNA damage. They exposed PC 12 cells to an Aβ (25–35) in frame and scrambled at 50 mM concentration for 24 hours to 50 hours. Oxidative damage of mitochondrial DNA was assessed using a Southern blot technique and a mitochondrial DNA-specific probe recognizing a 13.5-kilobase restriction fragment. PC 12 cells exposed to Aβ exhibited marked oxidative damage of mitochondrial DNA as evidenced by characteristic changes on Southern blots, but not in cells exposed to the scrambled Aβ peptide, suggesting that Aβ peptide is responsible for mitochondrial DNA damage, and ultimately leading to mitochondrial dysfunction in AD (Bozner et al., 1997).

Further, evidence from a recent gene expression study (Reddy et al., 2004) suggests that mutant APP or Aβ may generate free radicals and promote mitochondrial dysfunction, one or both of which may lead to oxidative damage. Altered levels of mitochondrial enzymes have been found to be directly responsible for a decrease in energy production in the brains of late-stage AD patients (Reddy et al., 2006). Soluble or insoluble forms of Aβ have been suggested to impair ATP production by generating defects in mitochondrial energy metabolism and oxidative stress (Behl et al., 2005). Taken together, these results suggest that oxidative stress is a key event in AD pathogenesis.

The major species responsible for oxidative stress is the overproduction or ROS and RNS, a major source of which is mitochondrial dysfunction (Zhu et al., 2007). ROS, which include superoxide radical anion and hydroxyl radicals are involved in the damage of lipids, DNA, and protein modifications. Minor modifications of the nucleic acid bases are repaired through base excision repair involving DNA glycosylase and AP endonuclease, which are located in nuclei and mitochondria. The progression of AD is associated with the diminished expression of these DNA repair enzymes (Nakabeppu et al., 2004). The accumulation of the oxidatively damaged nucleic acids and proteins likely exceed the limit of cellular repair and detoxification mechanisms and leads to the onset or progression of diabetic and

neurological pathologies. In general, accumulation of oxidatively damaged proteins, lipids, and nucleic acids correlate with the onset of age-related diseases, especially in diabetes and AD (Stadman et al., 2001), indicative of one and the same common pathological mechanisms.

Increasing evidence suggests that mitochondrial dysfunction and oxidative stress play a crucial role in the majority of neurodegenerative diseases. Mitochondria are a major source of intracellular reactive oxygen species (ROS) and are particularly vulnerable to oxidative stress. Oxidative damage to mitochondria has been shown to impair mitochondrial function and lead to cell death via apoptosis and necrosis. Because dysfunctional mitochondria will produce more ROS, a feed-forward loop is set up whereby ROS-mediated oxidative damage to mitochondria favors more ROS generation, resulting in a vicious cycle. It is now appreciated that reduction of mitochondrial oxidative stress may prevent or slow down the progression of these neurodegenerative disorders. However, if mitochondria are the major source of intracellular ROS and mitochondria are most vulnerable to oxidative damage, then it would be ideal to deliver the antioxidant therapy to mitochondria.

In the literature on AD, the terms “oxidative stress” or “oxidative damage” are commonly used to explain the balance between the production of oxidants and the endogenous antioxidant defenses in neuronal cells. In general, cells undergo apoptotic death when there is an imbalance between oxidants and antioxidants (more oxidants than antioxidant defenses). This oxidative damage mainly occurs via the mitochondrial ETC (Reddy et al., 2006).

There is mounting evidence to suggest that in late-onset AD, age-related free radicals, which are generated in the mitochondria, are carried to the cytoplasm where they activate beta secretase and facilitate the cleavage of the APP molecule (Reddy et al., 2006). The cleaved APP molecule (ie, Aβ) further generates free radicals, leading to the disruption of the ETC and enzyme activities, the inhibition of ATP, and the subsequent oxidation of both nuclear and mitochondrial DNA proteins. The damage caused by mitochondria ultimately leads to neuronal damage, neurodegeneration, and cognitive decline in AD patients (Reddy et al., 2006).

When obesity persists for a long time, antioxidant sources can be depleted, decreasing the activity of enzymes such as superoxide dismutase (SOD) and catalase (CAT). The activity of SOD and glutathione peroxidase (GPx) in individuals with obesity is significantly lower compared with that in healthy persons, having implications for the development of obesity-related health problems (Ozata et al., 2002). A study in rats showed that the liver concentration of vitamin A having antioxidant activity was significantly lower in rats with obesity compared with those without obesity; the concentration of vitamin A in rats with obesity probably indicates the dilution of this fat-soluble vitamin in high liver lipid storage (Capel et al., 1984). In addition to vitamin A, levels of serum antioxidants, such as vitamin E, vitamin C, and β-carotene, as well as glutathione, are decreased in obesity (Vincent et al., 2005). In addition to this, ROS decrease the expression of adiponectin, suggesting that treatment with antioxidants or ROS inhibitors could restore the regulation of adipokines (Furukawa et al., 2004). Thus, supplementation with antioxidants would reduce the risk of complications related with obesity and OS (Higdon et al., 2003).

Findings from clinical and experimental studies show that chronic accumulation of reactive oxygen species in older brains may exhaust antioxidant capacity and trigger neurodegenerative processes as characterized in AD. Thus dietary supplementation with fruit or vegetable extracts high in antioxidants help to decrease the enhanced vulnerability to oxidative stress and improve neuronal communication via increases in neuronal signaling and animal behavior (Joseph et al., 2009). Onset of AD was significantly delayed by use of antioxidant vitamins and polyphenols derived from fruits and vegetables (Luchsinger et al., 2007). Results from the Kame Project suggest that drinking fruit juices which are high in polyphenolic compounds, was associated with lower risk of incident AD (Luchsinger et al., 2007). Congruent with the notion that vascular health is key to maintaining cognitive function polyphenols from wine, cocoa, coffee, grape seed, blueberries, strawberries, tea, curcumin, pomegranate and green leafy vegetables also have beneficial effects on endothelial function and cardiovascular performance (Luchsinger et al., 2007). The beneficial actions of resveratrol have been implicated in anti-oxidant defence, regulation of the cell cycle, mitochondrial energy production, vascular reactivity, oncogene suppression and activation of sirtuins (silent information regulator-related enzymes), as anti-ageing inhibitors (Markus et al., 2008).

Accumulating evidence suggests changes in lifestyle factors such as increasing physical activity will decrease the risk of developing dementia in later life (Flicker et al., 2009). Most studies (Rovio et al., 2008) studies show reduced rate of age-related cognitive decline, decreased risk of incident dementia or AD in individuals who exercise regularly.

There are no known curative or preventive measures for most types of dementia. Diet and lifestyle could influence risk, and studies suggest that midlife history of disorders that affect the vascular system, such as hypertension, type 2 diabetes, and obesity, increase the risk for dementia including Alzheimer's disease (AD) (Luchsinger et al., 2004; Whitmer et al., 2005). Increased trends in demographic transition and urbanisation within many developing countries are predicted to lead to lifestyle changes (Ineichen et al., 1998). Delaying of onset, by modifying risk or lifestyle, decreases the prevalence and public health burden of dementia; a delay in onset of 1 year would translate to almost a million fewer prevalent cases in the USA (Brookmeter et al., 1998). However, this in turn might increase demands on health services and costs for older populations (Brayne et al., 2007).

Surprisingly, countries in Latin America, such as Venezuela and Argentina, bear a higher burden of over 5% prevalence of dementia. By contrast, a systematic analysis of six Indian studies suggests low prevalence (2–3%) of all dementias, with marginally fewer cases in urban compared with rural areas and in the northern versus southern states (Das et al., 2006). Pooled analysis of 25 Chinese studies by Dong and colleagues, (Dong et al., 1980-2004) comprising a total population of more than 76 000, suggested that the overall prevalence of dementia was 3.1%, indicating a significant rise from 1980 to 2004. However, a recent survey of over 34 807 Han Chinese residents aged at least 55 years in 79 rural and 58 urban communities of four distant areas reported a crude prevalence estimate of 5.0%, and 6.8% after adjustment for negative screening (Zhang et al., 2006). Higher prevalence was apparent in northern regions compared with the south, but no difference was evident among urban and rural Chinese residents (Zhang et al., 2006). In the Upper Assiut region along the Nile, age-adjusted dementia prevalence in people aged 65 years and older was 5.9% (Farrag et al., 1998). In the Yoruba (Niger-Kordofanian people) of Nigeria, dementia prevalence was low (2.3%) compared with an African American population in Indiana, USA (8.2%) (Hendrie et al., 1995). Among Arabs living in Wadi Ara, a community south of Haifa in Israel, the crude prevalence estimate for all dementias was 21% in those aged over 60 years (Bowirrat et al., 2001). Consanguinity among families was suggested as a reason for this high prevalence (Bowirrat et al., 2001). Studies from developing countries in Eastern Europe have assessed some risk factors, but prevalence or incidence data in these communities are unknown (Suhanov et al., 2006).

Multiple epidemiological studies have demonstrated a remarkable overlap among risk factors for cerebrovascular disorder and sporadic, late-onset AD (Jellinger, 2010; Kalaria, 2010). For example, mid-life diabetes (Knopman and Roberts 2010), hypertension (Iadecola and Davisson, 2008), and obesity (Whitmer et al., 2008) have all been shown to increase the risk for both AD and vascular dementia. It is now generally acknowledged that most AD cases have mixed vascular pathology and small-vessel disease (Jellinger, 2010). Moreover, reduced brain blood perfusion (Ruitenberg et al. 2005), silent infarcts (Vermeer et al., 2003), and the presence of one or more infarctions (Snowdon et al., 1997) all increase the risk of AD.

On the one hand, illiteracy or low educational achievement has been shown to be a robust risk factor for dementia (Borenstein et al., 2006). On the other hand, intellectually stimulating, socially engaging, or physical activities might lower the risk of dementia (Fratiglioni et al., 2004). The situation is not different in developing countries, where surveys have consistently identified low education as a risk factor for dementia (Ampil et al., 2005). However, in some communities, level of education, indexed by years of primary schooling, might not necessarily contribute to low prevalence (Hendrie et al., 2006). Low literacy is often linked to poverty or lower socioeconomic status, which is also associated with poorer health, lower access to health care, and increased risk of dementia (Keskinoglu et al., 2006.)

CONCLUSIONS

Alzheimer's disease is the most common cause of dementia late in life, affecting approximately 8 percent of people who are 65 years of age or older. Increasing frequency of vascular disease and global trends in modernisation will add to the burden of AD within developing countries. Harmonisation of screening methods worldwide could help to define risks and to devise novel approaches for dementia prevention. The impact of dementia in developing countries deserves further epidemiological and implementation research to enable early detection, widespread adequate treatment, and caregiver support. Such efforts will no doubt promote greater awareness, refine the policy agenda, and lead to a call for concerted action.

Recent advances in molecular, cellular, and animal model studies have revealed that mitochondria are the major source of free radical generation and of oxidative damage in aging and age-related neurodegenerative diseases. It is possible that age-related mitochondrial abnormalities and oxidative damage are major contributing factors for late-onset AD. To stop or delay the progression of late-onset AD, and also to reduce disease symptoms, several therapeutic strategies have been developed, including anti-inflammatory, antioxidant, and antiamyloid approaches. Among these, mitochondrial antioxidant therapy reduces AD pathology more than any other approach.

Adipose tissue is a secretory organ of great importance for the organism because the substances that it secretes meet the requirements for specific biological functions. As obesity is characterized by excessive storage of adipose tissue, adipokine secretion is increased; therefore, the effects produced in the body are altered, and resistance to its effect can be generated, as in the case of leptin. In addition to adipokines, we also found an overproduction of ROS, which damage cellular structures and trigger, together with underproduction of NO, progressive accumulation of fat and, eventually, the development of other pathologies. On the other hand, it was observed that the decrease in body fat reflected in weight improves oxidation markers and increases antioxidant activity, which was impaired with obesity. Therefore, weight loss through nutritional and pharmacological treatment, in addition to supplementation with antioxidant nutrients such as vitamins E, A, and C, flavonoids, among others, may be the key to reducing the risk of developing other pathologies related with OS and obesity.

Obesity is a condition that is epidemic and that has increased in recent decades. Parallel to the increase of this disease, the study of obesity has undergone considerable development. This has been accomplished thanks to research in

various fields of knowledge that have broken down multiple archetypes, allowing changes in views on overweight, adipose tissue function, and the pathophysiology of the disease that prevail at present. The breakdown of old paradigms and the new knowledge platform provide a solid foundation for understanding the disease and for developing strategies for prevention and treatment.

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[1]Faculty of Biology, University of "Alexandru Ioan Cuza" Iași, Romania,
[2]University of Medicine and Pharmacy "Gr.T.Popa" Iasi
ELENA-LOREDANA SANDU "Alexandru Ioan Cuza" University of Iasi, Faculty of Biology
0755 254 796; e-mail: lori_chem89@yahoo.com