Alzheimer's Dementia. The Influence of Oxidative Stress in Its Pathophysiology. Can the Antioxidant Glutathione Delay or Prevent Cognitive Impairment of Alzheimer's Disease?

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Article

Alzheimer's Dementia. The Influence of Oxidative Stress in Its Pathophysiology. Can the Antioxidant Glutathione Delay or Prevent Cognitive Impairment of Alzheimer's Disease?

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Abstract: Dementia from Alzheimer's disease (ADz) is an enormous and growing healthcare problem. The economic and societal burden of caring for those who develop Alzheimer's dementia (ADm) is rising as the population of those over 65 years of age increases. Current treatments are given to manage symptoms or to reverse established pathological insults of ADm. Evidence is presented that oxidative stress (OS) may initiate and promote the development of ADm when ADz is asymptomatic and that the antioxidant, glutathione (GSH), can counter OS. A novel nano-product, the glutathione-cyclodextrin (G-C) complex can effectively deliver GSH. It is proposed that if GSH is administered early in ADz to asymptomatic individuals with ADz it should delay or prevent the development of Adm. The complex is a topically applied non-prescription product that has no significant adverse side effects. As of 2023 GSH has not been studied in any current clinical trials. [1] Rigorous studies will be needed confirm its efficacy. If proven, its use should reduce the burden of ADm. **Background/Objectives**: Given the limitations of the current management of Alzheimer's disease (ADz), an approach of preventing Alzheimer's dementia (ADm) by using glutathione to counter oxidative stress is discussed. **Conclusions**: Oxidative stress may initiate and drive the deposition of amyloid-beta plaques and formation of neurofibrillary tangles that results in ADm. Rather than focusing on their removal, preventing their formation may be a more cost-effective strategy of ADz management. Unless treatments of ADz are discovered that are more effective than what is currently available, the cost of ADm management may reach up to $ 1.5 trillion by 2050. Evidence is presented that glutathione (GSH), supplied via a nano-compound, the glutathione-cyclodextrin (G-C) complex, may counter OS and delay or prevent the development of ADm. If future studies confirm this concept, the complex should significantly reduce the healthcare burden of ADm.

Keywords: Alzheimer's disease; Alzheimer's dementia; oxidative stress; reactive oxygen species; antioxidant; glutathione; glutathione-cyclodextrin complex; nano-technology

1. Introduction

The economic and societal impact of ADm cannot be understated. In 2023, there were an estimated 6.2 million imdividuals in the United States with ADm and a projected increase to 12.7 million by 2050.[1] Given that the incidence increases with age and as the elderly population grows, the direct cost of healthcare of those with ADm in the US in 2020 was 196 billion and estimated to increase to $1.5 trillion by 2050 unless significant interventions or managements are developed.[2] The indirect healthcare cost is estimated to be another 254 billion.[2] In addition to the cost of providing care to an individual with ADm, the physical, emotional, psychological, and workplace impact on the family members and other caregivers is immeasurable. Treatments that can delay or prevent the onset of ADm would be the most cost-effective approach to ADz management. There is growing evidence that oxidative stress (OS) is an early initiator and driver of the pathophysiologic process of ADm. Thus, early intervention in ADz by reducing oxidative stress (OS) may mitigate the

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progression to ADm. Evidence will be presented that this may be accomplished using a novel nano-product, the G-C complex, that therapeutically delivers the antioxidant, GSH. Hopefully, this will encourage its use in rigorous studies to confirm its efficacy. Although the pathophysiology of ADz progression is complex and not completely understood, the complex could play a critical role in the management of ADz by delaying or preventing ADm. If future studies support the efficacy of GSH, its use will reduce the socio-economic burden of Adm.

2. Glutathione (GSH), Reactive Oxygen Species (ROS) and Oxidative Stress (OS) in Human Diseases

As our primary intracellular antioxidant, GSH is integral in maintaining our health and well-being against the negative effects of oxidative stress (OS). [3] OS occurs when our biological system creates excessive ROS (and to a lesser extent, reactive nitrogen species (RNS)) that alter the normal homeostatic balance between pro-oxidant and anti-oxidant molecules. ROS and RNS are produced in response to external stimuli. Although ROS is beneficial at physiologic levels, its excess leads to OS. At a physiologic level, ROS regulates aging and activates the innate inflammatory response. [4] This innate response, in turn augments the secondary adaptive immune response. [5] As signaling molecules, ROS and RNS regulate or mediate many physiologic functions. These include gene activation, cellular growth, and blood pressure control. [6] Under adaptive physiologic conditions, excessive ROS can be controlled by enzymatic (superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic (glutathione) antioxidants. Glutathione (GSH) is well-established as the most important cellular antioxidant. [3,7–10] ROS is primarily generated in mitochondria, but it is also produced in peroxisomes, endoplasmic reticulum, and lysosomes. [6] The duality of ROS in diseases, whether physiologically beneficial or pathologically harmful, has been outlined. [11] The "Goldilocks" concept of adaptive vs deleterious ROS response using an exercise model has been presented. [12] The level of ROS, which in excess leads to deleterious OS, appears to be the determining factor in disease progression. [13,14] OS and GSH deficiency are also associated with advanced age and diseases of the brain, heart, lungs, eyes, liver, kidneys, and of the nervous and vascular systems. [3,7,11,13,15–18]

2.1. Glutathione Deficiency and Oxidative Stress in Neurodegenerative and Neurologic Disorders

GSH deficiency and OS have been associated with many neurodegenerative and neurologic illnesses, including ADz, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), multiple sclerosis, and autism spectrum disorders. [19–30] Aoyama et al. reviewed the association of neural GSH deficiency with ADz, PD, and ALS. [21] Algahtani et.al., described the association of mitochondrial dysfunction and OS in AD, PD, HD, and ALS. [31] Underscored was the role of GSH in counterbalancing OS.

Using proton magnetic resonance spectroscopy (^{1}H-MRS) to detect GSH levels *in vivo*, evidence was presented of GSH deficiency in the brains of AD, PD, and ALS individuals. Expressly, a lower level of GSH was noted in the temporal and parietal lobes of older adults, with a negative correlation of GSH levels to Aβ levels as assessed with positron-emission tomography (PET) imaging. In PD, there is post-mortem evidence of decreased GSH levels in the substantia nigra of the midbrain. Finally, again using ^{1}H-MRS, a decrease in GSH levels was noted in the motor cortex and corticospinal tract of individuals with ALS. [21] A serum marker of OS is malondialdehyde that is ia bypoduct of lipid peroxidation. [32]

2.2. The Glutathione-Cyclodextrin Complex

There is evidence that a novel nano-product, the GSH-cyclodextrin (G-C) complex, can effectively increase GSH levels and counter OS. [32] With this complex, GSH is sequestered in gamma-cyclodextrin (γ-CD) and is administered topically. It therefore avoids the degradation of oral GSH, the cost and inconvenience of intravenous GSH, and the limitations of converting N-acetyl

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cysteine (NAC) into GSH. [8,9,15,33,34] In contrast to the G-C complex, NAC does not increase GSH levels unless there is a depletion of GSH and presence of a functional enzymatic pathway for *de novo* synthesis of GSH. [35]

3. Alzheimer's Disease

3.1. Societal and Healthcare Impact of Alzheimer's Dementia

The impact on the quality of life and healthcare cost of ADm is enormous. It currently affects over 50 million individuals worldwide. A statistical review in 2020 of the impact of ADz in the United States presented the following data: 1) the direct cost was $305 billion and without significant improvement in AD management, was predicted to grow to more than $1.1 trillion by 2050, 2) 70% of the lifetime cost of caring is borne by families, 3) as of 2018, AD was the fifth leading cause of death for those aged 65 years or older, 4) 1 of every 3 seniors who die in 2020 (roughly 700,000) will have ADm. [36] An updated overview in 2024 presented additional statistics: 1) 6.9 million (10.09%) of people age 65 and older has Alzheimer's dementia, 2) a yearly amount of unpaid healthcare help by one's family in 2023 was estimated to be 18.4 billion hours or nearly 31 hours of care per caregiver per week with an estimated economic value of $232 billion and does not account for the physical, emotional, psychological, and workplace toll on those caregivers that is immeasurable, 3) in 2023, Medicare and Medicaid covered $231 billion (64%) of direct healthcare cost plus $91 billion (25%) in out-of-pocket spending with an estimated total cost of $360 billion, and 4) claims-based changes in ED visits between 2008 and 2018 had an increase of 28% for AD, followed by 26% for heart failure, 23% for stroke, and 14% for ischemic heart disease. [37]

3.2. Alzheimer's Disease Pathophysiology

Alzheimer's disease is a neurodegenerative disorder with neuropathologic hallmarks that include deposition of amyloid beta (Aβ) as plaques, formation of neurofibrillary tangles (NFT), synapse and neuronal loss, neuroinflammation, neurotransmitter deficiencies, and reactive gliosis that eventually leading to cognitive impairment. [38] In addition to the pathologic Aβ deposition and NFT formation, the earlier influence of glial mediated neuroinflammation is becoming more apparent.

There is evidence of the influence of mitochondrial dysfunction and OS early in ADz progression, including elevated levels of OS markers. [39,40] These markers include an increased level of malondialdehyde (MDA), a lipid peroxidation product, early in ADz. [41] Prior to the development of lecanamab, the treatment of ADz with disease-modifying therapies had been disappointing. [42–45] However, arguments against coverage of lecenamab has been presented upon reviewing its cost vs its modest benefit and potential risks. [46] In addition to neurotransmitter enhancement, disease management has been mainly directed against Aβ deposition and NFT formation. This approach may address ADz at a point of the disease process that is difficult to modify or reverse. That is, the development of ADm may be more complex than strictly the result of Aβ plaque deposition and NFT formation. [47,48]

Rather than treating ADz-associated damage to neurons, avoiding the insults of Aβ and neurofibrillary pathology may be more effective by preventing their development. Aβ accumulation in the brain triggers chronic inflammation which in turn, promotes the further progression of ADz pathology. [45,48]

Cheong et al. highlighted the complex disease process that is not completely understood. The current disease hypotheses include the processes of amyloid cascade deposition and tau formation, and of the excitatory and cholinergic activity that prompt current therapeutic interventions. [49,50] The sub-optomtimal response to these treatments are likely due to underscored by a combination of factors, including:1) treatments are initiated after dementia symptoms are present and significant pathology is established, 2) not all individuals with Aβ plaques or NFT develop dementia, and 3) autopsy studies have documented the absence of Aβ and NFT in some individuals who fit the clinical criteria of Alzheimer's dementia.[37] Notably, the cost of a currently approved and most promising

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treatment, lecanemab, is $26,500 per person per year and is given to symptomatic individuals. At present, there is no accepted therapeutic intervention for asymptomatic ADz persons. [51] There are many reasons for this dilemma 1) although newer non-invasive measures seem promising, currently acceptable early detection methods of asymptomatic ADz are expensive (with PET scans) or invasive (with CSF analysis) and are not available for routine clinical use, 2) administering treatment to asymptomatic persons requires the need for an intervention that does not present additional significant risks, 3) not all people with positive biomarkers develop dementia, and 4) since ADz begins 20 years or more before onset of dementia symptoms, prevention of ADm necessitates the prolonged use of a safe and cost-effective treatment. [37]

Acknowledging the current problematic side effects and limited efficacy of current therapies, potential treatments may need to be redirected and focus on the influence of glial cells (microglia and astrocytes) that promote neuroinflammation earlier in the pathophysiologic process of ADz prior to Aβ deposition and neurofibrillary tangle formation [45,52] The complexity of neurodegeneration and the influence of inflammation (incuding its heightened risk with advancing age) on microglia and astrocytes are described in detail. The influence of decreasing ROS to facilitate the elimination of Aβ and reducing the neurotoxicity of soluble Aβ was described.[52] The influence of the inflammatory cascade in Aβ deposition and Tau pathology was also outlined. Significantly, the listing of pharmacological treatments of AD did not include GSH. [45]

Kern et al. recently identified a plasma protein biomarker, placental growth factor (PlGF), that may be used to identify individuals at risk for developing ADm. [53] PlGF is a member of the vascular endothelial-derived growth factors. It is related to cerebral small vessel disease, T2 white matter intensities and vascular cognitive impairment and dementia. If confirmed as a biomarker, it would avoid the cost of ^{1}H-MRS or PET scanning and the invasiveness of cerebral spinal fluid analysis. PlGF apparently plays a role in vascular permeability that is associated with cognitive decline. It expands our knowledge of ADz pathophysiology but also exposes our incomplete understanding of the disease process.

3.3. Alzheimer's Dementia Treatments

Current treatments of ADm attempt to reverse established pathology or treat symptoms rather than address the early, underlying process that causes dementia. Neurotransmitter treatments to improve cognitive function include the use of memantine, donazepril, rivastigmine, and galantamine. [50,54] Given the equivocal and disappointing results of Aβ and NFT treatment and the limited response to neurotransmitter therapy, the need for early alternative approaches to address the underlying pathophysiology and impede ADz progression has come into focus by addressing Aβ homeostasis, not in its removal, but preventing its deposition. [55] Although a more recent monoclonal antibody (lecanemab) shows some promise in early ADm, a multimodal approach may be more efficacious, that is, to also target the chronic neuroinflammation attributed to activated microglia and astrocytes that produce numerous pro-inflammatory cytokines. [48,54,55] In a detailed review on the influence of microglia in ADz, the Miao et al. recommended focusing future therapeutic approaches on targeting neuroinflammation and OS prior to the onset of ADm.[48] This may need to address ADz early, at its pre-clinical stage with treatments that are directed against OS. [47,56–59] The obvious barrier to this early approach is having methods to identify those at-risk individuals before symptoms of dementia are evident. [38] Encouragingly, early markers and imaging methods have been identified. These include PET scans, functional or proton magnetic resonance imaging, AD associate gene markers, ocular imaging, and MDA. (kern)[21,22,38,60–66] The measurement of a particular combination of CSF biomarkers has a sensitivity of 95% and specificity of 83% and is used in clinical trials to detect individuals who will develop ADm. [42] Unfortunately, these interventions are still research tools and are not yet available in routine clinical practice due to their cost, access, or invasiveness. Ocular examination as a non-invasive method for early AD detection has been proposed. [53,62,67–69]

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OS has been recognized as the initial and a driving force in Aβ deposition, and Aβ in turn, may be a compensatory response to OS. [41,67,70] The scientific conundrum of which came first, Aβ or OS, would be a moot issue if early reversal of OS prevents Aβ deposition and neurofibrillary tangle formation before their burden causes clinical symptoms. [40,58,71] Since the pathophysiology of ADz is complex and not fully understood, it warrants the studies of alternative disease mechanisms and the use of combination therapies. [47,49,66,72–77]

In a detailed review, Walker et al. described the role of peripheral inflammatory insults that increase the future risk of developing Alzheimer's disease. [78] The incidence of early dementia in persons with Down syndrome and its link with ADm was reviewed in a special issue edited by Salehi et al.[79] Another risk factor is age-related immunosenescence, which leads to upregulation of inflammation. The group further describes the subsequent deterioration of the blood-brain barrier (BBB) that would allow cross-talk of the peripheral with the central nervous system inflammatory events. They propose that ADm can be a result of an acute or chronic inflammatory process. Acutely by triggering innate immune activation and chronically through chronic cytokine expression. [78] Through several meetings of the Alzheimer's Association Research Roundtable, it was affirmed that clinically meaningful treatments need to either slow the decline or prevent future impairment. [80] The current limited treatment to slow the progression of ADm may prompt a greater focus on its prevention. Nevertheless, providing medication to prevent the onset of dementia raises not only the medico-economic challenge of establishing an accurate and cost-effective method of identifying persons with heightened dementia potential but also the accepting the cost and the risk vs benefit of treating an asymptomatic individual. [46,78,81,82]

4. The Influence of Microglia in Neuroinflammation and ADz Progression

Aβ aggregates induce activation of microglia (the resident macrophages of the central nervous system). [48,54,55] Activated microglia, in turn, exacerbates Aβ accumulation in a positive feedback loop. Pro-inflammatory cytokines have also been shown to encourage the formation of NFTs. [54] As ADz progress, the beneficial phagocytic actions of the activated microglia decrease while its inflammatory actions increase. The influence of mitochondrial dysfunction and OS was also discussed as well as the vulnerability of the brain to ROS in driving ADz pathophysiology. In a review of the many Aβ-related small molecule treatments listed by Zhang et al. for ADz, GSH was not included.[55]

5. The Significance of $A\beta_{42}$ in Alzheimer's Dementia Cognitive Decline

In a recent retrospective analysis of 24 clinical trials, it appears that newer anti-Aβ drugs that can slow the cognitive and clinical decline in ADz are associated with an increased level of $A\beta_{42}$ (an Aβ isoform) in the cerebral spinal fluid.[83] of nearly 26000 subjects. This includes studies with lecanamab. Conversely, drugs that lower $A\beta_{42}$ levels (eg. verubecestat) worsen cognition and functional performance in AD patients. Developing drugs that raise $A\beta_{42}$ levels offers another therapeutic target for ADm treatment beyond the removal of Aβ plaques.

6. Discussion

The socio-economic impact of ADz is enormous and growing. Its direct monetary impact is over $300 billion and is projected to reach over $1 trillion unless successful interventions are discovered. Except for the recently approved monoclonal antibody, lecanamab, disease modification of ADz has been disappointing. Despite its promise, the use of lecanamab is initiated after the presence of cognitive impairment and its cost-benefit is in question. A more effective management of ADz would be to prevent the onset of ADm. A potential approach may be to addresss the pathophysiologic processs of ADz that leads to ADm

The role of OS in ADz has not been thoroughly studied. This is partially the result of the absence of an effective antioxidant available for clinical use. Due to the inverse relationship of OS with GSH

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levels, either due to age, metabolic status, or from acute or chronic illness, a deficiency of GSH appears to result in OS. Evidence has been presented that a novel nano-product, the G-C complex, can effectively increase GSH levels and counter OS. [32] Hopefully, the ability to deliver GSH directly with the complex will encourage studies to determine the efficacy of exogenous GSH to mitigate OS in ADz. GHS deficiency may not only be related to aging but restoring GSH may be a potential therapeutic target to treat ADz.

However, the use of GSH in the presence of OS in ADz requires answers to several questions: 1) is OS only an associative biomarker? 2) is OS a significant initiator and promoter of ADz? 3) is OS present in ADz as a result of GSH deficiency? 4) Can GSH be restoration mitigate OS? and, 5) can the early use of the G-C complex to supply GSH to prevent the progression of ADz and avoid ADm? Regardlesss of the incomplete understanding of the pathophysiologic process of neuroinflammation from microglial activation, suppressing OS with the G-C complex may mitigate the progression to dementia. It appears that the complex does not need to directly address the initiating pathology, but instead, the subsequent physiological response of OS. Finally, providing therapeutic levels of exogenous GSH may address the pathophysiologic processes and insults of ADz before severe or irreversible injury occurs.

Due to the inverse relationship of OS with GSH levels, either due to age, metabolic status, or acute illness, a deficiency of GSH appears to result in OS. Given this premise, restoring GSH should reverse OS. Studies with other antioxidants have been problematic, equivocal, or disappointing. [84,85] Most studies use weak antioxidants, and NAC is a GSH precursor that requires endogenous enzymatic conversion into GSH. Experimental antioxidants (e.g., superoxide dismutase) are not available for clinical use. Finally, immunotherapeutic agents are costly. It is proposed that the transdermal G/C complex can effectively deliver exogenous GSH. The complex has advantages over other antioxidants and treatments. Through nanotechnology, it 1) delivers GSH in a measured amount, 2) avoids the delivery problems of oral and intravenous GSH, 3) does not need enzymatic conversion.

Given the complexity and uncertain nature of the complete pathophysiology of ADz, a multimodal approach would be advisable. Although newer antibody therapies (eg, directed toward raising $A\beta_{42}$ levels) seem encouraging, they are costly and are initiated to reverse or slow existing cognitive decline. A more cost-effective approach should target the pre-clinical stage of ADz. Administering GSH through the G-C complex may provide that approach. Its benefits are that it: 1) is safe, 2) has a low cost as it is not a monoclonal antibody, 3) modulates but does not suppress the immune response, 4) is a commercially available non-prescription product that does not require special storage, 5) is easily administered as a topical agent and 6) should complement existing therapies.

7. Conclusions

Alzheimer's dementia is an enormous and growing healthcare problem. As the population of those over 65 years of age increases, the cost care of those with ADm is estimated to grow to $1.5 trillion unless significant interventions or managements are developed beyond what exists today. Lecanamab, the most promising disease-modifying medication now available has received criticism that its limited benefits may not justify the cost or added health risks from its use. This reflects our current incomplete knowledge of the pathophysiology of ADz that can direct development of disease-modifying therapies to treat ADm. Preventing the onset of dementia may be more effective target than of interventions to reverse the existing pathology of Aβ deposits and NFTs. A proven treatment to prevent the onset of dementia currently does not exist and needs to address obstacles that include: 1) the development of a cost-effective and non-invasive clinical marker that can identify asymptomatic individuals at risk for developing ADm, 2) having a low cost that justifies it use for possibly decades, including to some individuals with a positive marker who may not develop ADm, and 3) exhibiting a benefit that outweighs its risks. Providing GSH may be that treatment. Evidence has been presented that OS may initiate and promote the development of ADm. GSH, a potent

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antioxidant, can counter OS. GSH has been successfully sequestered in γ-cyclodextrin to form the transdermal nano-product, the G-C complex. This complex can overcome the current difficulty of delivering GSH therapeutically. Although there are no existing clinical trials with GSH, hopefully, the availability of the G-C complex will prompt those studies. If its efficacy is confirmed, the complex may significantly reduce the socio-economic burden of ADm.

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Abbreviations

The following abbreviations are used in this manuscript:

ADz	Alzheimer's disease,
ADm	Alzheimer's dementia
Aβ	amyloid beta
NFT	neurofibrillary tangles
OS	oxidative stress
ROS	reactive oxygen species
RNS	reactive nitrogen species
GSH glutathione	
G-C complex	glutathione-cyclodextrin complex
PD	Parkinson;s disease
ALS	amyotrophic lateral sclerosis
HD	Huntington's disease,
^{1}H-MRS	proton magnetic resonance spectroscopy
PET	positron-emission tomography
NAC	N-acetyl cysteine
PlGF	placental growth factor

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