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Biomarkers, ketone bodies, and the prevention of Alzheimer's disease

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ABSTRACT

Sporadic Alzheimer's disease (spAD) has three successive phases: preclinical, mild cognitive impairment, and dementia. Individuals in the preclinical phase are cognitively normal. Diagnosis of preclinical spAD requires evidence of pathologic brain changes provided by established biomarkers. Histopathologic features of spAD include (i) extracellular cerebral amyloid plaques and intracellular neurofibrillary tangles that embody hyperphosphorylated tau; and (ii) neuronal and synaptic loss. Amyloid-PET brain scans conducted during spAD's preclinical phase have disclosed abnormal accumulations of amyloid-beta (Aβ) in cognitively normal, high-risk individuals. However, this measure correlates poorly with changes in cognitive status. In contrast, MRI measures of brain atrophy consistently parallel cognitive deterioration. By the time dementia appears, amyloid deposition has already slowed or ceased. When a new treatment offers promise of arresting or delaying progression of preclinical spAD, its effectiveness must be inferred from intervention-correlated changes in biomarkers. Herein, differing tenets of the amyloid cascade hypothesis (ACH) and the mitochondrial cascade hypothesis (MCH) are compared. Adoption of the ACH suggests therapeutic research continue to focus on aspects of the amyloid pathways. Adoption of the MCH suggests research emphasis be placed on restoration and stabilization of mitochondrial function. Ketone ester (KE)-induced elevation of plasma ketone body (KB) levels improves mitochondrial metabolism and prevents or delays progression of AD-like pathologic changes in several AD animal models. Thus, as a first step, it is imperative to determine whether KE-caused hyperketonemia can bring about favorable changes in biomarkers of AD pathology in individuals who are in an early stage of AD's preclinical phase.

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1. Introduction

Sporadic Alzheimer's disease (spAD) is the most common cause of dementia in the United States, being responsible for 60% to 80% of dementia cases [1]. Viewed from a temporal perspective, the illness can be divided into three successive phases [2]: (i) pre-clinical (pcAD), which is asymptomatic; (ii) mild cognitive impairment (MCI); and (iii) dementia (ADd). The three phases and the presumptive biomarker trajectories that accompany them [3] are modeled in Fig. 1.

The principal histopathological features of spAD include (i) extracellular cerebral amyloid plaques, consisting largely of aggregates of amyloid-beta (Aβ), cerebral amyloid angiopathy, intracellular neurofibrillary tangles (NFTs), which embody abnormally phosphorylated tau protein (p-tau) in the form of paired helical and straight filaments [4], and glial responses;

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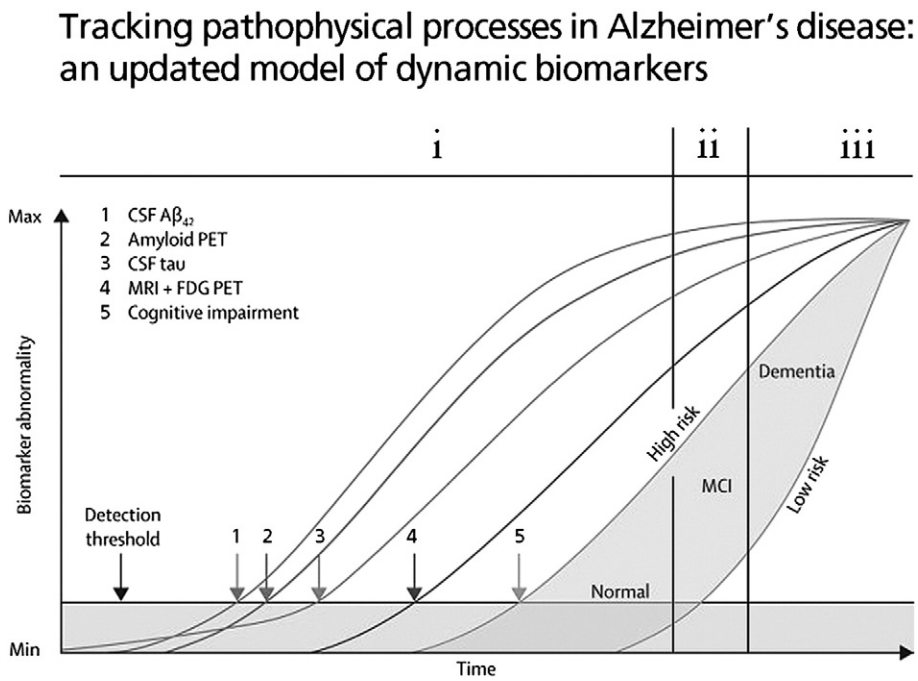

Fig. 1 – Evidence of Aβ42 abnormality is detected in the cerebrospinal fluid (curve 1) early in Phase i [preclinical phase]. Next, accumulation of amyloid deposits in the brain is disclosed by amyloid-PET scanning for amyloid content (curve 2). At the same time abnormalities of tau and phosphorylated tau (p-tau) may be detectable in the CSF (curve 3). In Phase i and during Phase ii (mild cognitive impairment [MCI]), selective decreases of the brain's glucose metabolism (cerebral metabolic rate of glucose [CMRglu]) have been demonstrated by FDG-PET(curve 4). CMRglu reduction may occur many years (even decades) before cognitive deterioration emerges in *APOE* ε4-positive and other high-AD-risk individuals. Independently, structural magnetic resonance imaging (sMRI) studies (also in curve 4) show atrophy of key areas of the brain concerned with memory and cognition, such as the hippocampus. Cognitive performance is designated by curve 5, which includes the shaded area under the curve. By the time the Phase iii [dementia] appears, cerebral deposition of Aβ (curve 2) will have slowed or ceased. Thus, in Phase iii, the rate and severity of memory loss, loss of executive function, and confusion, are better reflected by progressive changes in t-tau and p-tau, FDG-PET and sMRI. (Adapted from C.R. Jack, Jr., et al., Lancet Neurology 2013 [3]. Reproduced with permission from the publisher.)

and (ii) neuronal and synaptic loss [5]. For the most part, amyloid plaque builds up before cognitive deficits are identified, while neurofibrillary tangles, and neuronal and synaptic loss match progression of cognitive decline [3]. Over time, these brain lesions and accretions become extensive, and are associated with a seriously disrupted neuropil [5].

Tau proteins are expressed in 6 different isoforms in human adults, and belong to the category of microtubule-associated proteins (MAPS). Tau proteins are abundant in central nervous system (CNS) neurons. One of their important functions is to incorporate α- and β-tubulin monomers into neuronal microtubules (MTs) [6,7]. Thus, tau plays a major role in maintaining MTs in a state of dynamic stability. MTs direct specific membrane traffic in neurons and have recently been found to regulate dendritic spines—the major sites of excitatory synaptic input. MTs systematically leave the dendritic shaft and enter dendritic spines, modulating spine morphology. Such alterations appear to make a major contribution to synaptic plasticity and help maintain and control synaptic activities involved in memory formation and cognitive functions [8]. An insufficiency of synapses appears to be responsible for the memory impairment manifested in early AD [9]. Inhibition of α-tubulin deacetylase (HDAC6) activity has been reported to promote microtubule stability [10]. However, when tau becomes abnormally hyperphosphorylated (p-tau), as occurs in AD, its ability to support microtubule integrity is lost and the tubules deteriorate. The outcome of this disruptive process is the increasing synapse deficit and accumulation of insoluble aggregates of NFTs, hypothesized to play a major role in the causation and progression of AD [11].

2. Sporadic AD's predementia phases

2.1. *Preclinical spAD*

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) developed diagnostic guidelines for spAD and, in particular, pcAD. Three preclinical stages were proposed: (i) asymptomatic amyloidosis; (ii) asymptomatic amyloidosis + neurodegeneration; and (iii) amyloidosis + neurodegeneration + subtle cognitive decline [2]. The pcAD workgroup stressed the importance of examining the factors that best predict the risk of progression from normal cognition to MCI and ADd. To this end, the need to conduct longitudinal studies in spAD endophenotypes was emphasized [12].

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2.2. Mild cognitive impairment (MCI)

Data from the Alzheimer's Disease Neuroimaging Initiative have been used to assess the utility of magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) biomarkers as predictors of one year progression from amnestic MCI to ADd. During this relatively brief period, the spAD signature cortical thickness MRI biomarker performed better than hippocampal volume and CSF tau, which, in turn, was a better predictor than CSF Aβ. Over a longer three year time-to-event interval, transition from MCI to dementia was best predicted by the combination of the MRI and CSF biomarkers [13]. Mapstone et al. have identified a biomarker panel of 10 plasma lipids, which includes 8 phosphatidylcholine (PC) species. This panel was able to predict conversion, within 2 to 3 years, of cognitively normal elderly people to MCI or AD dementia [14].

3. Biomarkers are essential for an understanding of AD's nature and evolution

Definitive diagnosis of AD can only be made from an examination of tissue samples from AD patients taken during brain surgery, brain biopsy, or at autopsy. Thus, in cognitively normal individuals who are carriers of one or two *APOE* ε4 alleles [15] or whose risk of developing spAD is enhanced for other reasons, such as having prediabetes, type 2 diabetes mellitus [T2DM], or a history of parental spAD [16,17], it is necessary to rely on biomarkers to disclose the likely presence of prodromal AD during the disease's long and symptom-free preclinical phase.

When a specific treatment becomes available that offers a reasonable possibility of arresting, reversing, or slowing progression of pcAD, it is critically important to be able to detect the presence of early, latent AD in individuals at high risk of developing the disease, and then to find ways to obtain convincing evidence that the treatment being tested is having a meaningful beneficial effect. One way to acquire such evidence would be to carry out prospective, longitudinal studies in which serial measurements of appropriate biomarkers are used to assess the effect of the test intervention in groups of individuals with prodromal AD.

It is also urgent to determine whether a given intervention can prevent or delay conversion to dementia in individuals with MCI. For most of its victims, MCI is the last stop on the road to dementia. For individuals so afflicted, it is not currently possible to be sure how long it will take for dementia to supervene. Given this uncertainty, if a potentially effective intervention is available, it should be implemented without delay.

4. Apolipoprotein E

Apolipoprotein E (apoE) in humans is polymorphic, consisting of three major isoforms, apoE2, apoE3, and apoE4 [18]. Each isoform is encoded by a different allele (epsilon [ε] 2, 3, and 4). ApoE ε4 (*APOE4*) is the strongest genetic risk factor for AD and it can have significant modulating effects on AD biomarker levels and trajectories. For example, sex modifies the *APOE4*-related risk of developing AD [19]. Compared to age-matched ε-4 negative controls, elderly individuals who carry an ε4 allele exhibit a significant reduction in cerebral utilization of glucose, notably in the posterior cingulate, precuneus, lateral parietal and inferior temporal areas of the brain [20]. In AD, biomarker data cannot be properly interpreted in the absence of concurrent information about the subject's *APOE4* status [21].

5. Use of biomarkers to assess effectiveness of preventive intervention

In 2010, C.R. Jack, Jr., et al. [22] published a hypothetical model of the major biomarkers of spAD that described the temporal evolution of the biomarkers in relation to each other and to the onset and progression of clinical symptoms. In the model, updated in 2013 [3], five well-established AD biomarkers were divided into two major categories, as follows: (i) measures of brain Aβ deposition: (a) cerebrospinal (CSF) concentrations of Aβ42, and (b) distribution of cerebral Aβ deposits and their relative concentration, as determined by positron emission tomography (PET) amyloid imaging, and (ii) measures of neurodegeneration: (a) CSF concentrations of total and phosphorylated tau (t-tau and p-tau); (b) presence and degree of cerebral hypometabolism quantified by [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET); and (c) atrophy disclosed by structural MRI (sMRI).

The AD biomarker model described by Jack et al. [3,22] makes it possible to view in one arena rates of change of each biomarker, the curves that describe their trajectories, and the order in which the different biomarkers become abnormal (Fig. 1). Because of the experience already gained with this integrative approach, consideration should be given to using a similar model to test the effects of a new intervention in AD phenotypes while they are still in an early stage of the illness's preclinical phase.

6. Hypotheses that purport to explain spAD's pathogenesis

Of the many theories that have been proposed to explain why and how spAD evolves, two will be addressed herein. They are (i) the amyloid cascade hypothesis (ACH) [23–25], and (ii) the mitochondrial cascade hypothesis (MCH) [26–28]. The ACH has been accepted – at least provisionally – by most AD investigators for many years. Indeed, the ACH has provided most of the targets for new drug research [29,30]. On the other hand, the more recently proposed MCH seems to cover in greater number and detail consequential issues relevant to AD's pathophysiology, including some about which the ACH has been frustratingly vague.

6.1. The amyloid cascade hypothesis (ACH)

The ACH was first described by Hardy and Higgins in 1992 [23]. Two important observations formed the basis of the ACH: (i) identification of Aβ as the principal constituent of AD's "senile plaques" (now known as *amyloid* plaques), and (ii) discovery of mutations of the *APP*, *PSN1* and *PSN2* genes in families with autosomal dominant (ASD) amyloid angiopathy associated with cognitive and histopathologic

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changes typical of AD [31,32]. PSN1 and PSN2 proteases appear to be involved in the γ-secretase complex that sequentially cleaves the amyloid precursor protein, (APP), yielding the 37–49-amino acid peptide, amyloid beta (Aβ) [33]. In ASD angiopathy, mutations in each of these proteins may be responsible for shifting APP processing toward the formation of Aβ42, thereby promoting cerebral β-amyloidosis [34]. According to the ACH, cerebral deposition of Aβ42 is the trigger that sets AD's pathogenic process into motion, and then contributes to its progression to dementia and death [23–25]. Unfortunately, drugs or antibodies designed to target components of the amyloid cascade have (so far) failed in clinical trials, causing many AD investigators to reconsider their assumptions about the ACH [35].

6.2. *The mitochondrial cascade hypothesis (MCH)*

First described by Swerdlow and Khan in 2004 [26], the MCH makes the assumption that baseline mitochondrial function and durability are genetically determined. Mitochondrial durability influences the timing of the mitochondrial changes that occur in response to metabolic stress and advancing age. The resulting decline in mitochondrial function represents the primary underlying problem in spAD, initiating the pathophysiological events in the brain responsible for the biomarker changes measurable during AD's predementia phases. Thus, inheritance can affect AD risk by influencing mitochondrial function [36].

Despite their outward resemblance, autosomal dominant Alzheimer's disease (ASD AD) and spAD, have different etiologies. Thus, inferences based on information generated about the genetic defects and abnormalities in APP processing that are responsible for ASD AD, are not necessarily applicable to spAD, which lacks these particular genetic flaws [27]. ASD AD accounts for no more than 1% of total cases of AD [1]. Although it has been reported that Aβ perturbations can drive tau phosphorylation and tangle formation [37], the ACH is unclear about how this would work in spAD. In contrast, the MCH scenario postulates that reduced cell energy – a hallmark of mitochondrial dysfunction – promotes tau phosphorylation in both ASD AD and spAD [38].

6.2.1. *ACH does not satisfactorily explain the consistent association between age and AD risk*

Unlike the ACH, the MCH sees brain aging and AD as convergent, not divergent, processes. Clinical and biomarker studies show both cognitive decline and Aβ plaque accumulation to be common consequences and concomitants of aging, preceding dementia by about 12–19 years in one survey [39]. Studies of aging brain mitochondria have repeatedly reported reductions of complex I and complex IV (cytochrome oxidase) activity, together with increased generation of reactive oxygen species (ROS) [28]. Mitochondrial mutations accumulate with age and may promote aging [40]. Reduction of electron transport chain (ETC) enzyme activities favors increased production of ROS and oxidative stress which, by itself, has been implicated in both aging and the pathogenesis of spAD [41]. Mitochondrial dysfunction resulting from aging-associated mtDNA deletions promotes amyloid accumulation and brain atrophy in the APP/Ld transgenic mouse model of AD [42].

6.2.2. *When do the aging process and the AD pathogenic process diverge?*

The proponents of the MCH suggest that a physiologic divide between aging and spAD arises at the point where the body no longer has the ability to compensate for certain age-related operational failures, such as declining mitochondrial efficiency, manifested, for example, by impairment of ETC function. When this happens, maladaptive events are thought to occur, such as increased production and/or decreased clearance of Aβ42, oxidative stress, inflammation, and aberrant phosphorylation of tau [28].

7. Biomarker assessment of changes in mitochondrial function during pcAD

Studies of subjects with preclinical AD have disclosed brain insulin resistance and deficiency [43], decreased mitochondrial respiration, reductions in the activities of key metabolic enzymes (such as pyruvate dehydrogenase complex [PDHC] and α-ketoglutarate dehydrogenase [αKGDH]), and decreased cerebral glucose metabolism [44]. Impairment of cerebral glucose utilization, measured by FDG-PET, may occur decades before AD becomes clinically manifest, and the resulting bioenergetic deficit may contribute to the disease's pathogenesis [45].

Mitochondrial dysfunction associated with AD could also result in increased lactate formation, increased production of ROS, pro-inflammatory cytokines, and reduced ATP generation. The following metabolites (viewed as biomarkers), measured by nuclear magnetic resonance spectroscopy (NMRS), provide information about the brain's neuronal health [46]: (i) N-acetyl aspartate (NAA), when present in normal amounts, indicates neuronal and axonal integrity. Decreases in NAA levels indicate loss or damage to neuronal tissue, which may result from many types of brain insults. (ii) Creatine and phosphocreatine levels reflect the status of brain energy metabolism. Gradual loss of creatine may be indicative of tissue death resulting from neurodegenerative disease, injury, or ischemic hypoxia. (iii) An elevated brain lactate is a hallmark of aging (and presumably of AD as well). Using proton (^{1}H) MRS and high-performance liquid chromatography (HPLC), Ross et al. [47] found that brain lactate levels were increased twofold in both normally and prematurely aging mice. A concurrent investigation of the respiratory chain enzymes disclosed mitochondrial failure in key brain areas from both normally and prematurely aging mice during aging.

8. Ketone ester-produced vs. diet-induced hyperketonemia

Availability of certain ketone esters (KEs) suitable for oral administration will make it possible to safely raise plasma ketone bodies (KBs) to levels previously achievable only by prolonged fasting or strict adherence to a very-high-fat, very-low-carbohydrate ketogenic diet (KD) [48]. After the KE is hydrolyzed in the intestinal tract, the KB moiety (i.e. β-hydroxybutyrate) seamlessly enters the systemic circulation, becoming available for use by the CNS. This method for directly elevating plasma KB levels avoids the confounding metabolic

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effects associated with consumption of a nutritionally unbalanced KD. The human brain has been shown to utilize KBs in near proportion to their plasma concentration [49]. This hospitable treatment of KBs attests to their vital importance as the brain's principal alternative fuel.

9. Experimental elevation of plasma ketone body levels in AD animal models

Orally administered ketone monoester (KME) has been reported to reduce anxiety, preserve cognitive performance, and lessen amyloid and tau pathologies in a male 3xTg mouse model of AD. The KME diet decreased Aβ deposition in the subiculum and the CA1 and CA3 regions of the hippocampus and amygdala. Concurrently, levels of hyperphosphorylated tau were reduced in these same regions. The KME-treated animals also showed improvement in tests of memory performance [50]. Experimentally induced hyperketonemia has been shown to prevent synaptic dysfunction caused by mitochondrial respiratory complex (MRC) inhibitors [51]. The authors found that MRC inhibitors suppress both population-spike (PS) and field-potential amplitudes in the CA1 hippocampus. Pre-treatment with a ketogenic diet strongly prevents changes in the PS, whereas partial protection is seen in the field potential. The KD also acts as a neuronal antioxidant by increasing mitochondrial glutathione (GSH) levels in the hippocampus [52]. KD-fed rats show a twofold increase in hippocampal GSH, stimulating the activity of glutamine cysteine ligase (GCL), the rate-limiting enzyme in GSH biosynthesis. In this way, KD upregulates GSH biosysnthesis, enhances mitochondrial antioxidant status, and protects mtDNA from oxidant-induced damage.

Glutamate neurotoxicity appears to contribute to the neurodegeneration associated with glucoprivation of the brain and brain ischemia—conditions associated with elevation of glutamate levels in the CNS. Massieu et al. [53] found that the ketone body, acetoacetate (AcAc), efficiently protects against glutamate-mediated neuronal damage in the hippocampus of rats chronically treated with iodoacetate—a glycolysis inhibitor. Hippocampal cultured neurons exposed to iodoacetate are also protected by AcAc. The energy reduction caused by iodoacetate is capable of causing neuronal death. AcAc's protective effect was attributed by the authors to its role as an energy substrate that bypasses the iodacetate-induced blockade of glucose utilization by neurons. It is possible that the glucoprivation resulting from the reduction in cerebral metabolic rate of glucose (CMRglu), a hallmark of preclinical AD, is associated with damaging accumulations of glutamate in cognition-involved brain sites.

10. Experimental elevation of plasma ketone body levels in humans with MCI or ADd

Medium-chain triglyceride (MCTG)-induced elevation of ketones in humans with MCI or early ADd produces transient improvement in cognitive performance in some cases, particularly in individuals who are apoE ε4-negative [54]. MCTG ingestion usually produces a modest increase in plasma KBs from default levels of ≤0.2 mmol/L to levels of about 0.4–0.7 mmol/L about 1½ to 4 h later, depending in part on amount of MCTG taken and its ingestion rate. No reports are available on effect of MCTG consumption on biomarkers of mitochondrial function in high-risk individuals in the preclinical phase of AD. Given the much higher plasma KB levels attainable by oral administration of KE [55] (i.e., about 7 mmol/L vs. the ~0.7 mmol/L concentration obtainable with MCTG), it would be advantageous to study the effect of KE on mitochondrial biomarkers in asymptomatic, cognitively normal individuals whose risk of developing AD is substantially enhanced by possession of an apoE ε4 allele or a positive history for maternal spAD.

11. Conclusion

There is a near consensus that the most opportune time for preventive intervention in spAD is in the earliest stage of its preclinical phase (pcAD). At present, the only way to disclose the likely presence of pcAD is by means of appropriate biomarkers. It is also necessary to rely on biomarker-generated data, used as dependent variables, to assess the potential therapeutic efficacy of the intervention. The nature of the intervention chosen will depend in considerable part on the investigators' concept of AD's pathogenesis. Adherents of the ACH will tend to focus on treatments believed capable of protecting CNS neurons from damage inflicted by toxic forms of Aβ. Adherents of the MCH will emphasize treatments intended to restore impaired mitochondrial function and promote mitochondrial stability.

Studies have shown that, regardless of the ketone-raising modality employed, elevation of plasma KB levels can improve mitochondrial function and prevent or delay progression of AD-like histopathologic changes in various AD animal models. With the coming availability of KEs for oral administration, it will be possible to obtain badly-needed information about the relationship between plasma KB concentration and clinical response. The effect of raising plasma KB levels on AD biomarkers in people judged to be in the preclinical phase of AD has not yet been studied. Given the critical need for a prevention strategy that is at least partly successful in reducing the progression to dementia in AD-susceptible individuals, a trial of KE should be carried out in high-AD-risk individuals whose biomarker findings indicate that they are in AD's preclinical phase. As an initial step, the ability of KE treatment to induce favorable changes in biomarkers of AD pathology can be used to assess its potential effectiveness as an inhibitor of pcAD's progression.

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