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PERSPECTIVE

Targeting immunometabolic pathways for combination therapy in Alzheimer's disease

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Abstract

The recent success of disease-modifying anti-amyloid monoclonal antibodies in slowing Alzheimer's disease (AD) symptoms has been an exciting step forward for the field. Despite successfully clearing amyloid from the brain, however, only modest symptomatic improvement has been demonstrated, and treatment-related side effects such as amyloid-related imaging abnormalities (ARIA) limit use for some. These limitations suggest that fully efficacious AD treatment may require combination therapy regimens, as are used in other complex disorders such as cancer and HIV. One reasonable strategy may be to use agents that address the biological changes that predict future amyloid accumulation, or accompany amyloid accumulation in preclinical disease states. Immunometabolic pathways, including the insulin signaling pathway, are dysregulated at the earliest stages of AD, concomitant with amyloid accumulation. It is plausible that agents that target these pathways may work synergistically with anti-amyloid therapies to halt AD progression. Insulin signaling is integrally involved in innate and adaptive immune systems, with pleiotropic effects that moderate pro- and anti-inflammatory responses. Metabolic modulators that enhance insulin sensitivity and function, such as GLP-1 receptor agonists, SGLT2 inhibitors, and insulin itself have been shown to improve immune function and reduce chronic inflammation. Additional effects of insulin and metabolic modulators demonstrated in preclinical and clinical studies of AD include increased clearance of amyloid-β, slowed tau progression, improved vascular function and lipid metabolism, reduced synaptotoxicity, and improved cognitive and functional outcomes. A large number of compounds that treat metabolic disorders have been extensively characterized with respect to mechanism of action and safety, and thus are readily available to be repurposed for combination therapy protocols. Determining the most successful combination regimens of these agents together with disease-modifying therapies, and the appropriate timing of treatment, are promising next steps in the quest to treat and prevent AD.

KEYWORDS
Alzheimer's disease, amyloid, combination therapy, immunometabolic pathways, insulin

1 | INTRODUCTION

The therapeutic landscape for Alzheimer's disease (AD) has faced a prolonged drought, with no new therapeutic agents receiving FDA approval for nearly 30 years. This bleak situation brightened considerably, however, with the announcement of the first clearly positive Phase III trials of disease modifying anti-amyloid monoclonal antibodies, which normalized brain amyloid levels in a large proportion of treated participants, and slowed symptomatic progression by an estimated 30%.[1,2] The positive implications of these results cannot be overstated, and have been likened to the early days of therapeutics for cancer. The modesty of the clinical benefit provided by these agents despite successful clearance of amyloid also bears consideration, however, particularly in the face of documented risks such as amyloid-related imaging abnormalities (ARIA).

One such implication is that, although removal of amyloid may slow worsening of symptoms, it is not sufficient to halt symptom progression or induce improvement. An argument commonly advanced to explain this failure is that treatment needs to be initiated earlier. Ongoing trials in pre-symptomatic adults whose amyloid burden is successfully reduced will shed light on this possibility. Other compelling arguments, however, include the possibility that anti-amyloid treatments do not address upstream factors that lead to amyloid dysregulation in the first place, and which may exert their own pathologic influence prior to or in parallel with amyloid aggregation. These upstream factors may differ in sub-populations of patients. Additionally, removal of amyloid might need to be accompanied with upregulation of mechanisms that can facilitate repair of extensive damage inflicted over the course of the disease, or that reduce negative side effects of the treatments themselves.

The examples above raise the possibility that adding therapeutic interventions in conjunction with anti-amyloid agents will enhance clinical benefit, by addressing upstream drivers of pathology and symptoms, reducing side effects, and regenerating lost brain tissue and synapses. Combination therapy approaches are standard of care for many complex diseases and have been transformative in treatments for cancer and HIV. Indeed, many in the AD field have advocated for more aggressive efforts in this area. Complexities in the realm of modern FDA approval processes resulting in concerns about unanticipated side effects caused by combination regimens, and desire to advance only proprietary agents within individual pharmaceutical companies have slowed such efforts in AD, to the likely detriment of therapeutic progress.

Determining which classes of agents are the best candidates for combination therapy is a complex undertaking. One reasonable strategy may be to use agents that address biological changes that predict future amyloid accumulation or accompany amyloid accumulation in preclinical disease. One such set of changes that has been identified in multiple studies is dysregulation of immunometabolic pathways.

2 | METABOLIC AND IMMUNE DYSREGULATION ARE INTEGRALLY LINKED, AND OCCUR EARLY IN AD PATHOGENESIS

Immune dysregulation and chronic neuroinflammation, including activated microglia and sustained pro-inflammatory cytokine release, are widely considered key components of AD pathogenesis which contribute to neurodegeneration and exacerbate both amyloid and tau pathology.[3] Recent work highlights the co-occurrence of immune and metabolic dysregulation early in AD, which is detectable prior to the manifestation of clinical symptoms. A recent proteomic analysis of 2000 brains and 400 cerebrospinal fluid (CSF) samples from well characterized older adults revealed early dysregulation in pathways related to glial metabolism, changes that correlated with pathological and clinical progression from normal to asymptomatic and symptomatic AD.[4] Many of the proteins found to have the strongest relationships with AD, such as CD44, fatty acid binding protein 5, and secreted phosphoprotein 1 (Spp1) have been implicated in metabolic dysregulation and in particular have been related to dysfunctional insulin signaling.[5]

Identification of pathways involved in both immune function and metabolism at the earliest stages of AD bridges three extensive bodies of work: the first documents immune dysfunction and neuroinflammation in AD as both a response to AD pathology and a driver of disease progression[6]; the second documents insulin as a critical regulator of immune function, exerting anti-inflammatory as well as immune-enhancing effects[7,8]; and the third implicates metabolic impairment as a key feature of AD, in which defects in insulin signaling or availability dysregulate energy metabolism and immune function, and contribute to AD pathogenesis.[9]

Review of the extensive literature relating AD and immune function/neuroinflammation is beyond the scope of this Perspective, and has been summarized in recent comprehensive reviews that implicate both the adaptive and innate immune systems, as well as the complement system.[6] With respect to the innate immune system, under normal conditions, microglia serve as monitors that remove waste and other debris, preserving normal synaptic function and connectivity. The blood-brain barrier (BBB), blood-CSF barrier, and meningeal barrier protect the brain and serve as outlets for waste removal. Border regions not protected by the BBB such as the circumventricular organs and choroid plexus are an interface between periphery and central nervous system (CNS), allowing communication between peripheral and central systems to maintain homeostatic immune function. AD pathology disrupts this homeostasis, causing microglia and astrocytes to undergo reactive changes, and peripheral immune cells to infiltrate the CNS, which may exacerbate pathological conditions, producing a destructive cycle.

Microglia play a critical role in the innate immune response through expression of cytokines such as interleukin-1β (IL-1β) and effectors such as triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 has both immune and metabolic actions, and after binding to its receptor, activates key insulin signaling pathways, targeting PI3K,

MAPK, and mTOR. TREM2 activation may have beneficial effects early in the disease course, and detrimental effects at later stages. Astrocytes also play an important role in innate immunity, and insulin is critical for regulating astroglial energy supply and inflammatory response.[10] Other important innate immune effectors secreted by microglia and astrocytes include complement proteins and nuclear factor kappa B (NF-κB), which modulates numerous inflammatory genes.

AD is also characterized by a disrupted adaptive immune response, although these effects have been less studied. Increased numbers of T cells have been observed in AD CSF and brain. T cells are peripherally derived, and BBB damage may allow infiltration into the brain. Activated T cells then secrete proinflammatory mediators that promote transition of microglia to reactive states. CD8+ T cells have been observed adjacent to Aβ deposits in AD hippocampus and perivascular spaces.[11] Further, elevations in activated, late stage effector memory T cells have been observed in CSF from persons with AD.[12]

All key immune/inflammatory processes thought to be related to AD pathology have been linked to metabolism, and in particular, to insulin signaling.[13] As discussed in excellent recent reviews, extensive integrated crosstalk between immune and metabolic pathways is evolutionarily conserved — immune cells require intensive metabolic resources, and close linkages between immune and metabolic systems are needed to support immune function. Insulin receptors (INSRs) are located on all immune cells, and their expression increases in the context of immune cell activation to allow regulation of immune responses. Via its receptor, insulin acts directly on immune cells through activation of the PI3K pathway, which activates downstream targets Akt and mTOR, with corresponding activation of immune effectors; for example, Akt activates NF-κB, a key initiator of immune cell activation, and interacts with the tumor necrosis factor (TNF) and toll-like receptor pathways.[14,15] Insulin also upregulates IL-1β and induces macrophages to change polarization state from M1 to the anti-inflammatory M2 state.[16,17] Conversely, insulin-stimulated mTORC1 activation enhances metabolism that promotes pro-inflammatory M1 polarization. The ability of insulin to moderate both pro- and anti-inflammatory responses reflects its integral and context-dependent role in the immune system, in which both types of responses are essential to maintain immune homeostasis. For example, in rodent studies, intracerebroventricular insulin administration increased microglial activation and levels of IL-1β and Cox-2 in hippocampus, effects that were accompanied by enhanced performance during water maze testing.[18] In other experiments, insulin increased phagocytic activity and reduced TNFα and iNOS expression in microglia.[19]

Cells of the adaptive immune system, such as T cells, also have activation-dependent increases in the INSR, and both pro-and anti-inflammatory effects have been attributed to insulin that contribute to optimal T cell-mediated immunity. Insulin regulates programming of T cells, and disabling the INSR impairs T cell antigen response.[15,20] Circulating T cells are thought to gain entry to the brain at border regions, including the BBB, blood-CSF barrier, and meningeal barrier.[12] Conditions which compromise the integrity of border structures such as insulin resistance facilitate T cell penetration into brain parenchyma, and may contribute to observations of elevated T cells in AD brain.

The complement system bridges the innate and adaptive immune systems and enhances the response of innate immune cells, often in response to antibodies generated by the adaptive immune system. Increased levels of complement proteins have been reported in AD. An interesting recent theory is that activation of the complement membrane attack complex by anti-Aβ monoclonals together with microglial-induced vascular inflammation may underlie the occurrence of ARIA.[21] Insulin resistance is characterized by high levels of complement activation products, which are normalized by treatment with insulin sensitizers, suggesting a potential role for these agents in prevention of ARIA.[22]

All conditions in which insulin function is disrupted are characterized by immune system dyshomeostasis. For example, type 2 diabetes (T2D) is associated with increased levels of pro-inflammatory cytokines and chemokines, together with decreased chemotactic migration of immune cells and a deficient T cell response.[15,20] TREM2 has also been implicated in metabolic diseases; increased levels of soluble TREM2, the ectodomain released after proteolytic cleavage, are increased in insulin resistant adults, and have been related to impaired cognition in T2D.[23]

In addition to its integral role in immune regulation, insulin also has direct interactions with fundamental aspects of AD pathophysiology. These interactions support the rationale that metabolic modulators are promising candidates for combination therapy for AD. As will be discussed, some of these agents have been tested as monotherapy in AD and have not shown clear benefits. This does not rule out their potential use in combination therapy protocols. Borrowing from the cancer field, many adjuvant agents do not singularly improve cancer outcomes but may synergize with other agents or ameliorate adverse events. Similarly, metabolic agents may not be able to overcome the effects of established AD pathology, but may exert positive effects when such pathology is attenuated, or reduce ARIA. Below, we discuss the extensive interactions between AD pathology and metabolism that have relevance for design of combination therapy protocols.

3 | INSULIN AND AD PATHOLOGY: INTERACTIONS WITH Aβ

Insulin impacts AD pathology directly via its interactions with the amyloid-β (Aβ) peptide.[9] Insulin protects against Aβ synaptotoxicity and modulates clearance through effects on lipid metabolism and proteases such as insulin degrading enzyme and neprilysin.[9] Peripheral insulin resistance is positively correlated with brain Aβ deposition in frontal and temporal areas.[24] Further, peripheral insulin resistance in midlife predicts Aβ aggregation assessed by amyloid PET 15 years later,[25] and has also been associated with increased accumulation of Aβ over the course of 2 years in cognitively normal, Aβ positive adults.[26]

The association between Aβ and insulin resistance may be related in part to the propensity of oligomeric Aβ to bind to the INSR

and interfere with insulin signaling.[27] A second mechanism that has been recently identified involves INSR isoforms and beta-secretase 1 (BACE1). Long known as the protease responsible for Aβ generation, BACE1 has recently been shown to cleave the INSR in a manner that reduces its effector isoform and interferes with insulin signaling.[28] Higher plasma BACE1 levels and increased enzymatic activity have been documented in persons with T2D who show cognitive impairment.[29] In AD brain, BACE1 cleavage of the INSR was associated with markers of cerebrovascular insulin resistance and reduced LRP1 expression, with increased neuritic plaque density, and with vascular levels of neprilysin and insulin degrading enzyme.[28] Taken together, these findings suggest that insulin facilitates Aβ degradation and clearance, and that BACE1 interferes with these actions through its effects on the INSR. This possibility has important implications for AD therapeutic strategies. For example, insulin and other anti-diabetic treatments have been shown to restore INSR function and reduce BACE1 activity.[30] Such properties further support the incorporation of metabolic modulators into combination therapy protocols.

4 | INSULIN AND TAU PATHOLOGY

Insulin metabolism has been closely linked to tau. The intraneuronal aggregation of insoluble tau protein into neurofibrillary tangles is a hallmark of AD, and the progression of tau pathology correlates with the progression of AD symptoms. In normal physiology, insulin enhances Akt phosphorylation, leading to downstream inhibition of GSK3β activity; defective insulin signaling impedes this process and ultimately results in tau hyperphosphorylation. Conversely, tau also regulates insulin signaling through interactions with PTEN that inhibit the conversion of PIP3 back to PIP2, thereby contributing to pro-cognitive insulin signaling.[31] Thus loss of tau function or indirect mechanisms such as inflammation and oxidative stress that induce tau pathology may impair insulin signaling. Pathological tau accumulation leads to increased oligomeric insulin aggregation within neurons, which results in brain insulin resistance.[32] Clinically, *post mortem* analyses and ex vivo stimulation of brains of patients with AD and other tauopathies have also documented brain insulin resistance.[33] Given the cyclical link between tau pathology and insulin resistance, metabolic modulators may enhance anti-amyloid treatment effects on tau and potentially slow AD progression.

5 | THERAPEUTIC APPROACHES: INTRANASAL INSULIN

The multifactorial links between metabolism, immune function, and AD pathology suggest that metabolic modulators may be useful treatments for AD. A number of studies have examined repurposed anti-diabetic drugs in this context, and a brief summary of findings will be presented for each of the therapeutic classes below. As will be discussed, every intervention that improves insulin sensitivity and dysregulated metabolism has also been shown to improve homeostatic immune and inflammatory processes.

A promising area of work has investigated the use of intranasally-administered insulin (INI) to correct brain insulin dysregulation. Delivery with specialized devices can rapidly and directly transport insulin to the CNS, bypassing the periphery to avoid hypoglycemia, and other adverse systemic effects. Upon intranasal administration, insulin is transported from the highly permeable nasal mucosa to the CNS via rapid, extracellular bulk flow through the perineural spaces along the olfactory and trigeminal nerves.[34] Insulin can then diffuse into the subarachnoid space and move into the perivascular spaces of the cerebrovasculature, where it is then rapidly transported through the brain to its therapeutic targets.

INI has been investigated as a potential AD treatment in several clinical trials with promising results. A recent 18-month phase II clinical trial examined the effects of INI on cognition, function, brain structure, and CSF AD biomarkers in participants with mild cognitive impairment (MCI) or AD.[35] Two cohorts received insulin (40 IU regular insulin) or placebo daily using different intranasal delivery devices. Treatment with the device used by the primary cohort yielded no significant difference in cognition or CSF biomarkers between the insulin and placebo groups. In prespecified analyses of the cohort that used the second device, however, insulin treatment was associated with significantly better performance compared with placebo on the primary outcome, the Alzheimer Disease Assessment Scale – Cognitive Subscale, after 6 and 18 months of treatment. Insulin treatment also improved CSF Aβ42/Aβ40 and Aβ42/tau ratios. Further, the device cohort that showed clinical benefit with insulin treatment showed reduced progression of white matter hyperintensity volume,[36] a pathology that has been linked to inflammation and vascular injury either by amyloid or other factors. It has been suggested that maintaining white matter integrity may represent a strategy to prevent cognitive and functional decline, and that ARIA may damage white matter in part through inflammatory processes, suggesting that INI may potentially ameliorate this effect. Supporting this possibility, INI treatment altered the typical progression of inflammation and immune function markers seen in AD (IFN-γ, eotaxin, IL-6, MDC, IL-2). Insulin treatment-related changes in the cytokine IL-1β, a marker of microglia activation, were strongly correlated with changes in CSF biomarkers Aβ42, Aβ40, ptau-181, and total tau.[37]

More studies are needed to fully understand how INI improves clinical status, AD pathology, and immune function. In addition, the new area of intranasal drug delivery has yet to determine clearly what characteristics of delivery devices and administration protocols are necessary for successful delivery of target compounds. Taken together, however, results from these studies suggest that INI may slow the progression of AD pathology and symptoms, in part through an enhanced compensatory immune/anti-inflammatory response that modulates Aβ and tau pathology, or through effects on Aβ and tau that benefit this response, or both. Given these beneficial effects, INI may serve as an effective partner for AD disease-modifying therapies.

6 | OTHER METABOLIC MODULATORS: SGLT2 INHIBITORS

Although insulin is the oldest and most well-known treatment for metabolic disease, new agents have been developed that address metabolic and vascular consequences of insulin resistance through complementary mechanisms. Sodium-glucose co-transporter 2 inhibitors (SGLT2is) are an important new class of therapeutic compounds that have concomitant effects on metabolism, vascular function, and immune function in T2D and cardiovascular disease. As recently reviewed,[38] SGLT2is reduce hyperglycemia through inhibition of the SGLT2 transporter, blocking the reabsorption of glucose from the kidney back into the circulation, resulting in off-loading of glucose into urine. Reduced hyperglycemia in turn decreases peripheral hyperinsulinemia with a corresponding decrease in insulin resistance. Because the glucose lowering action is independent of insulin, there is no risk of hypoglycemia.

Striking beneficial effects of SGLT2is on vascular function have been documented.[39] Proposed underlying mechanisms include: (1) SGLT2is reduce sodium reabsorption, leading to downregulation of sympathetic activity, reduced blood pressure, and improved vascular function; (2) SGLT2is enhance endothelial cell function, resulting in vasorelaxation, and reduced arterial stiffness; (3) SGLT2is reduce inflammation and oxidative stress, promoting anti-inflammatory M2 macrophages, and reducing NF-$\kappa\beta$ and NLRP3 inflammasome activity.

SGLT2i effects on brain have been less studied than peripheral endpoints. SGLT2 has been identified in the hippocampus and in choroid plexus epithelial cells where it may play a role in CSF production and brain glymphatics.[40] SGLT2 expression in human brain is increased with traumatic brain injury and cerebral ischemia.[41,42] Preclinical studies indicate brain effects of SGLTis relevant to AD; in an AD/diabetic mouse model, empagliflozin reduced amyloid plaques, inflammation, and microhemorrhages, preserved cortical volume, and enhanced memory.[43] Empagliflozin also improves hyperglycemia, insulin resistance, and vascular dysfunction, all of which potentiate AD pathology.

In human studies, a recent report of >11,000 cases with T2D and dementia compared with >46,000 T2D controls found that SGLT2i treatment was associated with a 42% reduced risk of dementia, the largest effect of any anti-diabetic medication.[44] A recent open label study in cognitively normal older non-diabetic adults also showed that empagliflozin reduced cerebral glutamate levels assessed with magnetic resonance spectroscopy, and acutely increased markers of insulin signaling in neuronal origin-enriched extracellular vesicles.[46]

7 | INSULIN SENSITIZERS

Several insulin sensitizing compounds have been proposed to restore CNS insulin sensitivity, although definitive evidence of brain effects in humans is lacking. The biguanide metformin may be the most well studied, and is the first choice drug to treat T2D. In addition to its glucose-lowering effects, in in vitro studies, it inhibits proinflammatory responses such as NF-κB and YKL-40.[47] Interestingly, human studies have revealed mixed effects on inflammatory endpoints, that were less pronounced than for other diabetic treatments.[47] Similar divergence has been observed for cognitive effects in clinical studies of MCI. In a randomized placebo-controlled trial, 80 non-diabetic participants with MCI received metformin or placebo daily for 12 months.[48] No treatment-related differences were observed for the ADAS-Cog, CSF Aβ42, or cerebral glucose metabolism assessed with FDG-PET. Better performance was noted on a memory test for metformin-treatment participants, motivating a phase II trial that is currently underway (NCT01965756).

Insulin sensitizers such as PPARγ agonists have been shown to reduce inflammatory markers in adults with T2D, possibly by downregulating NF-κB.[47] Studies of effects on cognition in AD, however, had shown equivocal results. In a pilot study of 30 patients with MCI and mild AD, rosiglitazone improved memory and stabilized plasma Aβ42 compared with placebo.[49] However a phase III trial showed no effects on cognition or function.[50] A phase III placebo-controlled trial of pioglitazone to delay the onset of MCI and AD was terminated early due to lack of efficacy (NCT01931566). It has been suggested that failure to cross the BBB limits efficacy for these agents, or that off-target cardiovascular adverse effects offset potential benefits.[51]

In summary, there is limited human evidence that the insulin sensitizers tested to date enhance brain insulin sensitivity or can act as effective therapeutic agents in AD in isolation. However, the important question of whether such agents provide additive benefit when combined with anti-amyloid treatment is still viable. It is possible that once amyloid is removed, the potential to evoke normal brain insulin signaling would be restored, with resulting positive effects on symptom progression.

8 | INCRETIN MODULATORS: DPP4 INHIBITORS AND GLP-1 RECEPTOR AGONISTS

Incretin modulators such as DPP4 inhibitors (DPP4i) and GLP-1 receptor agonists stimulate insulin secretion in response to hyperglycemia and can thereby regulate glucostasis and improve insulin resistance that occurs as a result of chronic hyperglycemia.[52] They also have potent effects on immune regulation and inflammation through modulation of toll-like receptor 4-induced cytokine secretion, and NF-κB inhibition.[53] GLP-1 is found in the brain, where it may increase cell proliferation and growth, and protect against excitotoxic cell death and apoptosis.[53] A recent meta-analysis in human clinical trials of prediabetes and T2D found beneficial effects on biomarkers of inflammation and oxidative stress.[54] GLP-1 receptor agonists used to treat diabetes have been proposed as potential therapeutic options for AD. Evidence in preclinical models has been supportive. For example, in mouse and non-human primate models, liraglutide treatment preserved memory, increased hippocampal neuronal density, as well as protected against INSR loss, tau hyperphosphorylation, and synaptic dysfunction.[55] Human studies have been equivocal. A pilot study

of exenatide in 18 adults with early AD showed no effects on cognition or imaging and CSF biomarkers.[56] A small group of participants with AD treated with liraglutide for 26 weeks had non-significantly higher brain glucose metabolism compared with placebo, but no effects on cognition or Aβ burden were observed.[57] A phase II randomized placebo-controlled clinical trial of 12 month of daily liraglutide treatment in AD patients is ongoing (NCT01843075), and will examine treatment effects on FDG-PET as well as on cognitive performance. To date, no trial has examined effects of DPP4is in persons with AD.

9 | NON-PHARMACOLOGICAL APPROACHES

Lifestyle interventions targeting dietary patterns and physical activity have long been acknowledged as powerful modulators of metabolism and immune function, and more recently have been raised as possible preventative or therapeutic strategies for AD. Adults consuming Western diets that are high in simple carbohydrates and saturated fats have increased risk of developing AD compared to those consuming diets high in lean proteins and poly-unsaturated fats.[58] Conversely, meta-analyses of dietary interventions focused on increasing consumption of polyunsaturated fatty acids, nuts, and plant-based foods while limiting saturated fats, animal-derived proteins, and refined sugars have shown that higher adherence to this dietary pattern is correlated with greater peripheral insulin sensitivity, and with lower risk of AD and age-related cognitive decline.[59]

Although studies have documented that high fat diets impair brain insulin signaling in animal models,[60] few human studies have directly examined diet effects on measures of brain metabolism. In a randomized controlled trial in which cognitively normal and MCI groups consumed a high saturated fat/high glycemic diet or a eucaloric low saturated fat/low glycemic diet for 4 weeks, the low diet increased CSF insulin and CSF Aβ42 for the MCI group.[61] In another study, dietary restriction in obese or diabetic adults improved the brain response to INI.[62] Although the precise mechanisms through which these effects are mediated are likely multi-factorial, diet modulates many risk factors associated with AD such as brain and peripheral insulin resistance, inflammation, obesity, diabetes, and vascular disease.

The ketogenic diet (KD) may offer therapeutic benefit for AD because of its ability to improve mitochondrial function and cerebral bioenergetics, reduce neuronal hyperexcitability, enhance autophagy, and reduce oxidative stress. Further, a KD intervention in young adults produced lymphocyte changes associated with enhanced T cell immunity, increasing capacity of CD4+, CD8+, and regulatory T cells, and modulated cytokine production.[63] In a pilot trial of a modified Mediterranean ketogenic diet (MMKD) in MCI, the diet increased CSF Aβ42 and decreased tau and improved peripheral lipid and glucose metabolism (i.e., reduction of HbA1c, insulin, triglyceride levels).[64] Participants on the MMKD also showed increased cerebral ketone body uptake and cerebral perfusion. Ongoing clinical trials seek to confirm and expand these findings and will provide important information about the potential use of this powerful dietary intervention, and its effects on immune function in AD.

Exercise is known as the most effective modulator of peripheral insulin resistance and is being actively studied for the prevention of AD. Many insulin resistance-related risk factors for AD, such as hypertension and metabolic disease, can be prevented or treated through exercise. Similarly, exercise interventions have been demonstrated to positively influence markers of innate and adaptive immunity.[66] Although exercise improves brain insulin sensitivity in rodent studies, resulting in enhanced mitochondrial function, reduced oxidative stress, and reduced tau hyperphosphorylation and aggregation,[67] no human studies have examined the effects of exercise on brain insulin sensitivity. However, exercise has shown benefit as an adjuvant that increases the efficacy of cancer chemotherapies, and may offer similar benefits in AD.[68]

10 | TIMING OF COMBINATION THERAPY

An important question concerns the timing of combining interventions, and considerations may vary for different disease stages. For adults deemed to be at high risk to develop sporadic, late-onset AD, but who do not yet have established pathology, it is likely that most interventions would need to be given for years, if not decades, and the likelihood of developing disease although high is not certain; thus consideration of safety and feasibility are paramount. In such cases, reliance on medications to control co-morbid risk conditions, coupled with lifestyle interventions may be most appropriate as adjunctive therapies. Although such regimens might be described by some as only meeting current standards of care, there is in fact much to be learned before we can achieve truly personalized recommendations — comorbid risk conditions such as diabetes and hypertension have heterogenous pathophysiologies that respond to different drug classes. Similarly, response to dietary or physical activity regimens are highly individualized, and there is insufficient evidence to date to support personalized recommendations for AD primary prevention.

Secondary prevention in persons with established AD pathology but who are not yet symptomatic represents a promising area for combining immunometabolic modulators with anti-amyloid agents. Recent results of the Phase III lecanemab and donanemab trials showed that effective clearance of amyloid plaques was associated with slowing of progression, but effects were modest. Although trials with preclinical cohorts have not yet been completed, many would argue that given these recent findings, the degree of expected benefit is not likely to reverse or "cure" progression even at this stage of disease. Addition of immunometabolic modulators such as INI and other interventions may have multiple complementary effects as summarized in Table 1 and Figure 1: (1) Clearance of plaques and oligomeric/fibrillar/protofibrillar species of Aβ may prevent Aβ from occupying INSRs and allow more effective brain insulin signaling; (2) insulin signaling appears to promote amyloid clearance via its effects on vascular function, lipid metabolism and microglial function; (3) insulin mitigates synaptotoxic effects of amyloid, as well as promotes synaptic regeneration; (4) insulin inhibition of GSK3β could further slow tau progression; (5) demonstrated effects of insulin on CNS immune function could

TABLE 1 Mechanisms of metabolic modulators that may slow AD progression and reduce cognitive symptoms

Immunomodulator mechanisms	Proposed effects
Promotes clearance of amyloid[6]	Prevents Aβ from occupying INSRs,[11] enhancing brain insulin signaling and enhances synaptic function and regeneration[6]
Inhibits GSK3β activity[6]	Slows tau progression[16]
Improves vascular function[23] and lipid metabolism[6]	Improves amyloid clearance, bioenergetics,[28,44] slows WMH progression[20]
Regulates CNS immune function[21]	Regulates cytokine secretion and microglial function[6] to induce anti-inflammatory effects, slow neurodegeneration, possibly reduce ARIA
Restores CNS insulin signaling and INSR function[14]	Restores energy metabolism and overcomes insulin resistance to impede progression of AD pathology
Reduces BACE1 activity[13]	Blocks Aβ generation and INSR dysregulation[12]

Abbreviations: Aβ, amyloid-β; CNS, central nervous system; INSR, insulin receptor; WMH, white matter hyperintensity.

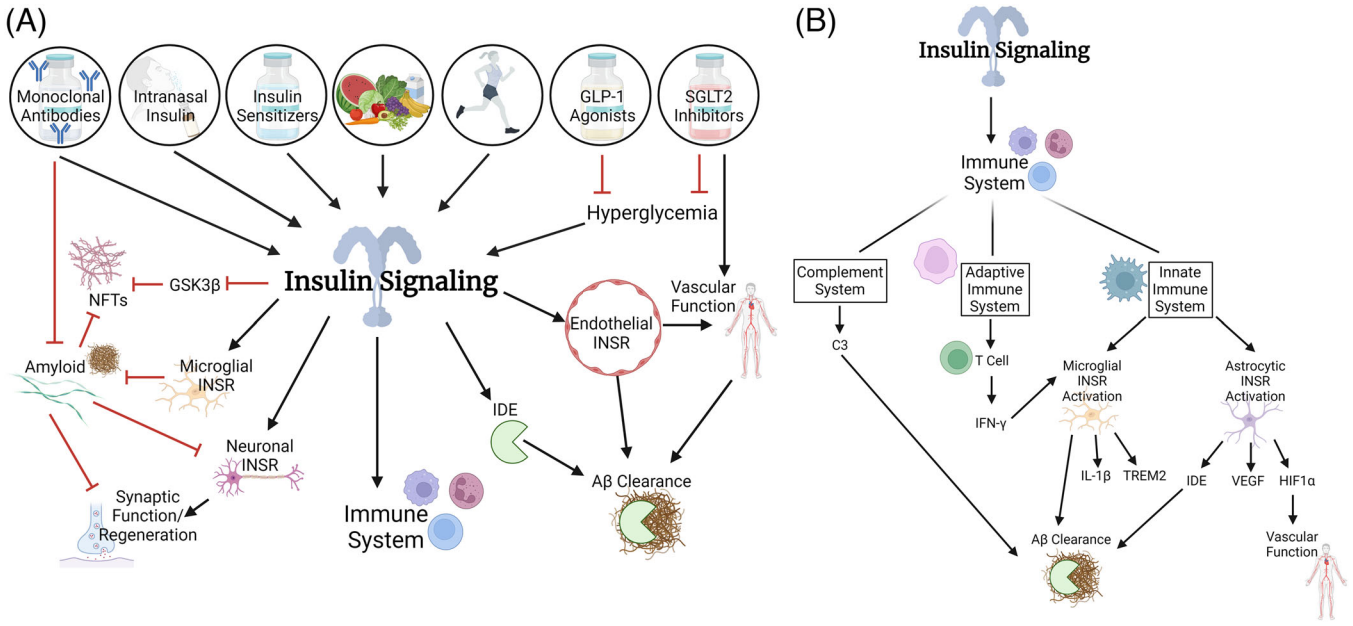

FIGURE 1 (A) Potential pathways and mechanisms through which immunometabolic modulation of insulin signaling affects processes related to AD and may be of benefit in combination therapy protocols; (B) Immune system pathways regulated by insulin signaling

synergize with anti-amyloid monoclonal antibody-induced immune response, potentially enabling lower therapeutic doses; (6) lower effective doses of anti-amyloid compounds and/or direct insulin-mediated effects on immunomodulation and vascular function may result in fewer adverse events, including lower rates of ARIA.

As with primary prevention efforts, the length of treatment is likely years. However, the probability of developing disease, while again not certain, is higher, tipping the scale in favor or more aggressive intervention. Thus, efforts to investigate whether immunometabolic modulators can increase efficacy, lower dosing, and reduce adverse events associated with anti-amyloid and other disease modifying therapies has a large potential pay-off. A similar case can be made for treatment of mild Alzheimer's dementia.

For pre-symptomatic and MCI stages, a priming or intermittent treatment approach may offer benefit without the risks of continuous long-term treatment. This approach is used in other medical fields; for example, treatment of newly diagnosed T2D with short-term intensive insulin treatment induced remission that lasted up to 1 year in nearly 50% of patients.[69] Similarly, intermittent KD intervention is used to manage epilepsy. Other questions relating to timing of therapy bear investigation — are immunometabolic modulators more effective as combination therapy when administered after amyloid has been cleared? Or do they reduce inflammation that might contribute to ARIA, suggesting that early treatment aligned with initiation of anti-amyloid therapy is most beneficial?

11 | CONCLUSION

Recent successes with anti-amyloid therapies in AD trials offer new hope for treating or preventing this devastating disease. Although many investigators have highlighted the need for combination therapy

approaches in the past, the basis for such claims has been largely theoretical. One major contribution of recent rigorous trials is the clear demonstration that although removal of amyloid is an important factor in slowing AD symptoms, it is insufficient to halt or reverse them, and it is accompanied by significant risks. The search for adjuvants to enhance efficacy and safety is imperative; agents that target early disease defects in metabolism and immune function are logical candidates. Numerous FDA-approved agents that modulate metabolism and immune function through effects on insulin signaling and other pathways of relevance to AD have been extensively characterized with respect to mechanism of action and safety, and are readily available to be repurposed for combination therapy protocols. Let us begin this promising and essential next step in the AD therapeutic journey.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

Informed consent was not necessary for this Perspectives piece.

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