Alzheimer’s disease presents a major challenge to the ageing population in Europe due to its high morbidity, mortality, and burden on the health system. Alzheimer’s disease is traditionally accounted for by the aggregation of misfolded structural proteins including β-amyloid peptides. An increasing body of evidence describes its aetiology from a metabolic perspective, as a result of impaired brain glucose utilisation and insulin sensitivity. Biochemical measures of insulin and insulin-like growth factor (IGF) resistance, oxidative stress, and metabolic dysfunction should be considered alongside β-amyloid neurotoxicity in the pathophysiology of Alzheimer’s disease. Currently, the diagnosis of Alzheimer’s disease in clinical practice is based upon criteria such as those found in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM IV). More sophisticated centres include neuropsychological and performance-based functionality testing, genetic screening, neuroimaging, and a panel of biomarkers proven to have limited predictive value. The limitation to timely and accurate diagnosis of Alzheimer’s disease is exemplified by the fact that post-mortem examination is the diagnostic gold standard. Advances in understanding the pathogenesis of this neurodegenerative process beyond the abnormal accumulation of β-amyloid precursor protein allow for exploration of novel diagnostic and therapeutic modalities. As mentioned, a growing body of research supports the notion that Alzheimer’s disease occurs as a result of metabolic dysregulation. Neuronal survival and signalling pathways within the brain depend upon tightly regulated glucose metabolism. Hence, brain insulin and IGF resistance allow for the initiation of a neurodegenerative cascade. Impaired IGF signalling and brain insulin resistance activate kinases that phosphorylate tau and lead to
expression and accumulation of \(\beta\)-amyloid precursor protein-\(\beta\).\(^2\) The accumulation of abnormal proteins leads to endoplasmic reticulum and mitochondrial stress, the generation of reactive oxygen species and activation of inflammatory cascades, which promote apoptotic pathways within neurons.\(^3\) Reduction in cerebral glucose utilisation is evident in early stages of Alzheimer’s disease.\(^2\) Suppression of brain insulin receptors within in vivo models leads to cognitive impairment, neurodegeneration, and features of Alzheimer’s disease exemplifying the detrimental consequences of impaired glucose uptake by neurons.\(^5\) Regions of the brain most vulnerable to neurodegeneration in Alzheimer’s disease are those with the highest expression of insulin and IGF receptors, such as the temporal lobe. Metabolic dysregulation including hyperinsulinaemia with or without diabetes mellitus along with peripheral insulin resistance has been shown to correlate with the development of Alzheimer’s disease. This phenomenon is supported by evidence of increased \(\beta\)-amyloid precursor protein-\(\beta\), elevation of inflammatory indices, formation of advanced glycation end products and reactive oxygen species within the brains of patients with hyperinsulinaemia.\(^6\)

**Metabolic syndrome and Alzheimer’s disease**

The development of both metabolic syndrome and Alzheimer’s disease occurs as a result of similar genetic, environmental and lifestyle predispositions.\(^4,6\) For example, Grodstein \textit{et al.} found that type II diabetes mellitus correlated with lower neuropsychological test scores and an increased duration of time with type II diabetes mellitus was associated with even poorer scores. However, hypoglycaemic therapy seemed to improve cognitive scores.\(^7\) Similarly, midlife obesity was found by Kivipelto \textit{et al.} to correspond with elevated risks of dementia and Alzheimer’s disease in late life, which was further increased by vascular risk factors.\(^8\) Such observations are crucial in guiding clinicians towards the aetiology of Alzheimer’s disease in order to develop more effective therapies to reverse or halt this neurodegenerative process.

Diagnosis of Alzheimer’s disease may be improved by including biochemical markers of peripheral insulin resistance, hyperglycaemia, hyperinsulinaemia, the accumulation of reactive oxygen species, and advanced glycated end products. Collectively, such abnormalities elucidate the potential for ongoing neurodegeneration. Dynamic functional plasma insulin tests and cerebrospinal fluid (CSF) assays of raised insulin levels have been shown to be elevated in Alzheimer’s disease compared to normal age-matched controls.\(^3\) This relationship is correlative to the severity of dementia, which strengthens its validity as a prognostic method.

Logical approaches to preventing Alzheimer’s disease from a metabolic perspective have been shown to be effective in several circumstances. Evidence suggests that insulin treatment delivered intranasally improves cognition and memory in clinical trial participants with mild cognitive impairment.\(^2\) Additionally, insulin-sensitiser drugs such as peroxisome proliferator-activated receptor (PPAR) agonists (which also possess anti-inflammatory and anti-oxidant properties in addition to enhancing glucose uptake and insulin receptor sensitivity) decrease cognitive impairment and neurodegeneration in diet-induced obesity and type II diabetes mellitus patients. However, a multifaceted approach to diminish oxidative stress and metabolic dysfunction along with insulin and IGF resistance will be required to truly ameliorate cellular injury imparted upon neurons by the progressively toxic cascade, which leads to dementia and subsequently Alzheimer’s disease.\(^3\)

Identification of novel pathophysiological processes implicated in the development of Alzheimer’s disease directs further studies towards ascertaining improved diagnostic and prognostic methods. Additionally, early experiments show promising results for preventing the onset and progression of Alzheimer’s disease through tight glycaemic control in type II diabetics and obese patients with insulin and IGF resistance.

**References**


