ABSTRACT

Alzheimer’s disease (AD) is a neurodegenerative disorder that causes progressive decline in cognitive abilities of a person. Oxidative stress is one of the main factors for the development of AD. The β-amyloid (Aβ) deposits and tau tangles in AD are the major source of reactive oxygen species (ROS) and causes oxidative damage to neurons. Selenium (Se), plays a key role in antioxidant defense by redox regulation of important enzymes. While Se levels are reported to decline with age, conflicting reports exist regarding the levels of Se in AD patients. Selenoprotein P (SeP) is a highly glycosylated, Se rich plasma protein. Aside from its role as a Se carrier protein, an antioxidative function of SeP has also been suggested. In postmortem brain tissues, SeP showed a significant association with Aβ plaques indicating its possible role in the pathology of AD. Reports on the levels of Se and selenoproteins in plasma and cerebrospinal fluid (CSF) of AD patients are limited. Hence, the study was aimed to analyse the role of Se and selenoproteins in blood and CSF of AD patients and to correlate their levels with the known pathological markers of AD viz Aβ42 and total tau.

Blood samples were collected from AD (n=45), Vascular dementia (VD) patients (n=45) and age matched healthy controls (n=55). CSF samples from AD patients (24) and controls (22) were collected by lumbar puncture by a neuro-physician. The levels of pathological markers of AD viz. Aβ42 and tau, along with the status of Se, selenoproteins viz. SeP, glutathione peroxidase (GPx), thioredoxin reductase (TR) and antioxidants were assessed in the blood and CSF of AD patients using suitable methods.

The results of the study revealed that plasma Aβ42 level was significantly higher (P<0.001) and total tau was significantly lower (P<0.01)
in AD patients compared to controls, whereas in CSF the Aβ42 levels was significantly lower (P<0.001) and tau was significantly higher (P<0.01) in AD patients, indicating accumulation of these proteins in brain leading to neurodegeneration. No correlation was observed between plasma and CSF levels of Aβ42 and tau. Receiver operating characteristic (ROC) curve analysis and meta analysis indicated that plasma Aβ42 and tau could not serve as a reliable markers independently for AD diagnosis. However tau-to-amyloid ratio could be used as a reliable marker for differentiating AD from controls with cutoff values of <3.35 pg/ml (sensitivity 71%, specificity 65%) in plasma and >0.88 pg/ml (sensitivity 79.2%, specificity 72.7%) in CSF.

Se levels in blood and CSF did not vary significantly between AD and control groups. Plasma SeP was significantly elevated in AD (P<0.001) compared to controls, indicating induced expression of SeP to counter the increased oxidative stress in neurodegenerative condition. However, the level of this protein in CSF was decreased (P<0.05) in AD compared to controls. No correlation was observed between plasma and CSF SeP indicating an independent regulation of this protein in plasma and CSF.

The activity of plasma GPx was increased in both AD and VD patients compared to controls, with a concomitant decrease in glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (P<0.001) activity. No difference in CSF GPx activity was observed between AD and controls while GR activity was significantly reduced. The activity of TR was significantly lower (P<0.001) in AD patients in both plasma and CSF. No correlation was observed between Se and activities of selenoenzymes with tau and Aβ42. The malondialdehyde (MDA) levels were significantly higher (P<0.001) in both plasma and CSF along with a significant decrease (P<0.001) in reduced glutathione (GSH) levels, indicating elevated oxidative stress and altered redox status in both forms of dementia.
Amyloid β (Aβ) peptides in plasma are transported into the brain by Receptor for Advanced Glycation End Products (RAGE). The binding of Aβ to RAGE causes an inflammatory cascade via NF-κB pathway and augment the disease condition. While evidence indicates an association between G82S RAGE polymorphism in the ligand binding domain and AD, no reports exists on the specific amino acids involved in RAGE-Aβ interaction and influence of RAGE polymorphisms on its interaction with Aβ interaction. The present study also analysed the interactions of different forms of Aβ42 peptide (monomeric: polar, apolar and fibrillar) with RAGE and the influence of polymorphisms (G82S, R48Q and R77C) in ligand binding domain of RAGE using an in-silico analysis.

The structures of RAGE ectodomain (3CJJ), monomeric forms of Aβ42 – 1IYT (apolar) and 1Z0Q and fibrillar (2BEG) were obtained from PDB. The structure of wild type RAGE and RAGE variants (G82S, R48Q, R77C) were generated using SWISS MODEL followed by molecular dynamics simulation in GROMACS. The lowest energy structures were then docked with Aβ42 peptides. The results indicated that RAGE interacted better with fibrillar form of Aβ42 peptide and G82S variant showed enhanced binding affinity of RAGE towards amyloid peptides leading to enhanced inflammatory response.

In the present study, analysis of plasma Se, selenoproteins and redox status along with pathological markers in AD patients indicated that tau-to-amyloid ratio along with GSH and plasma/CSF SeP could be used as a biomarker for AD diagnosis. A large co-hort study with age, sex and Apo E correction is warranted to validate their use in clinical diagnosis of AD.